

Characteristics of Childhood-Onset Systemic Lupus Erythematosus in Cape Town, South Africa.

By

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SPTGRA001



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Declaration

I, Graeme William Spittal, hereby declare that the work on which this research project is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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List of Abbreviations

ACLA	Anti-cardiolipin antibody
ACR	American College of Rheumatology
ANA	Antinuclear antibody
Anti-dsDNA	Anti-double stranded DNA antibody
Anti-sm	Anti-smith antibody
AVN	Avascular necrosis
C3	Complement component 3
C4	Complement component 4
CI	Confidence Interval
cm	Centimetres
CNS	Central nervous system
eGFR	Estimated glomerular filtration rate
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
FBC	Full blood count
g/day	Grams per day
GFR	Glomerular filtration rate
GLADEL	Grupo Latino Americano de Estudio de Lupus
Haem	Haematological system
Hb	Haemoglobin
ISN/RPS	International Society of Nephrology/Renal Pathology Society
KDOQI	Kidney Disease Outcome Quality Initiative
LN	Lupus Nephritis
mg/dl	Milligrams per deciliter
MSK	Musculoskeletal system
NHLS	National Health Laboratory Service
Pro	Prospective
Retro	Retrospective

SLE	Systemic lupus erythematosus
SLICC/ACR DI	Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
UK	United Kingdom
USA	United States of America
WCC	White cell count

Part A - Protocol

Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease characterised by the formation of antinuclear antibodies.¹ SLE is the most common autoimmune disease, with an estimation of incidence ranging from 2.0 to 7.6 per 100,000 and prevalence of 20 to 50 per 100,000.²⁻⁴ The proportion of these patients who present in childhood has been estimated at 15-20%.¹ The disease appears to be more common in Europe, Asia and the Americas than in Africa, but much higher in patients of African ancestry living in the United States, United Kingdom or the Caribbean Islands.⁵⁻⁷ The prevalence of SLE in adult Black South Africans has been estimated to be 12.2/100,000, though there are no accurate figures available for children in South Africa.^{8,9} Childhood-onset SLE in South Africa has not been well documented. Faller et al reported on a cohort of 36 patients from the Gauteng region of South Africa and suggested that this disease is being increasingly recognized in Black South African children as the socioeconomic and political landscape has shifted.¹⁰ There is a perception that SLE is more common in the Western Cape of South Africa than in other parts of the country and that the disease has a higher morbidity and mortality than is documented in other countries. The patient profile, disease characteristics, morbidity and complications have not been described in the Western Cape, which has a different genetic profile to other parts of South Africa.

Aims

We aim to document the disease characteristics, disease activity, morbidity and treatment practices in our cohort of patients with childhood-onset SLE from Cape Town, South Africa.

Methods

A retrospective folder review of all patients with Paediatric SLE seen at Red Cross War Memorial Children's Hospital and Groote Schuur Hospital will be done.

Clinical and demographic data will be retrospectively collected as per the data collection sheet in appendix 1. The diagnostic criteria using the American College of Rheumatology (ACR) criteria will be used to confirm the diagnosis of SLE (see appendix 2). In addition the System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) for SLE will be calculated at onset, 1 year disease activity, 5 year disease activity and at the last visit (see appendix 3).

Analysis of disease characteristics will be done for various subgroups and predictors for increasing damage or mortality will be investigated.

Ethical Considerations

The study will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

Benefits to Individual Patients. As this is a retrospective study there will be no direct benefit to patients in this study.

Benefits to the Community. By doing this study we hope to gain insight into SLE in South African children. This will have a beneficial spin off for the community as a whole.

Risks to Patients. There are no risk factors to the patient.

Investigations on Study Patients. No additional investigations will be done on study patients. Tests done at the time of treatment at the institution may be presented in the study.

Confidentiality. Patients with SLE will be identified from the hospital database. Their files will be drawn and the required information will be recorded in an electronic database under a study number or letter. A separate file will be kept linking the study

number to the patient. This information will be kept on a computer that needs a code to gain access to it. Only the principal investigator will have access to this computer.

Children as Research Subjects (why not adults or experimental animals). Data from adult studies cannot be applied to paediatric practice due to differences in the clinical course of the disease. Consequently data needs to be obtained from an appropriate sample of infants and children.

Consent. To obtain consent from parents in this population will be difficult and probably not possible in most cases. We feel that there is important information in this study and in the interest of benefit to the community at large would like to ask for a waiver of consent.

Budget. There are no costs associated with this study.

Conclusion

The findings will enable us to describe the characteristics, morbidity and mortality of the disease in our disease population and to critically consider our treatment practices, which may lead to further study or changes in our clinical practice to better serve our patients. We will also contribute to the understanding of our patient populations

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Part B - Literature Review

Background

Systemic Lupus Erythematosus (SLE) is a multisystem, inflammatory, autoimmune disease that is characterised by the formation of antinuclear antibodies.¹ It is the most common autoimmune disease with an estimated incidence ranging from 2.0 to 7.6 per 100,000 and prevalence of 20 to 150 per 100,000.²⁻⁵ Although more commonly presenting in adulthood, it is thought that childhood onset SLE is becoming increasingly recognized.⁶ Approximately 15-20% of SLE occurs before the age of 19 years.^{1,7,8}

There is a wide variability in disease presentation and course. It is known that SLE presents differently, not only in respect to age, but also depending on the ethnic background and gender of the patient.^{3,9-11} The disease appears to be more common in Europe, Asia and the Americas than in Africa, but much higher in patients of African ancestry living in the United States, United Kingdom (UK) or the Caribbean Islands.¹²⁻¹⁴ There is a female preponderance, but this is also known to vary according to age.^{3,8,15,16} The prevalence of SLE in adult Black South Africans has been estimated to be 12.2/100,000, although there are no accurate figures available for children in Southern Africa.^{17,18}

The diagnosis of SLE is a clinical and laboratory diagnosis based on the American College of Rheumatology (ACR) Classification Criteria for SLE (see Appendix 2). In 1982, the ACR established eleven criteria for the diagnosis of SLE, which were revised in 1997.^{19,20} Four of the eleven criteria are required to be present for the diagnosis of SLE to be confirmed. This criteria, however, was established mainly for use in scientific research, so some people, especially those with lupus nephritis or antiphospholipid syndrome, may have SLE without four of the criteria. SLE frequently presents with features other than those in the ACR criteria, for example fever, lymphadenopathy, photosensitivity and alopecia.

Childhood-onset SLE has a more aggressive course than adult-onset disease.²¹⁻²³ The disease in children more often has major organ involvement as a presenting manifestation, with renal, central nervous system and haematological problems predominating. Children with SLE appear to be more susceptible than adults to nephritis, and the nephritis itself seems to be more severe in nature.⁸ Renal disease contributes significantly to the long-term morbidity and mortality in children with SLE and is thought to be one of the main poor prognostic factors in childhood-onset SLE. A poor outcome has been noted particularly with diffuse proliferative nephritis.²⁴⁻²⁶ Renal disease secondary to SLE is reported to be present in 29-80% of paediatric SLE cases.²⁷ Reporting bias may be the cause of this wide variation in renal disease with many studies being based in Nephrology clinics. A more accurate figure may be of approximately 50% in a combined Nephrology/Rheumatology clinic.²⁸

The severity of the renal disease was highlighted by an early study on childhood-onset SLE from the UK in which 47.6% of patients had renal disease during the course of their follow-up. In these patients, none of the children without renal disease died, while in the patients with nephritis, the five- and ten-year survival was 59.5% and 47.6% respectively.²⁵ However, the association of renal disease and a poorer outcome has been refuted, even in those with advanced renal disease at presentation.²⁹

Outcome scoring for SLE is controversial. Deciding whether a child who has been diagnosed with SLE has a greater or lesser degree of disease activity and determining how to avoid disease damage are essential for patient management.

It is not possible to use one individual clinical sign or laboratory value to measure the progression of the disease. To help with this, indices of disease activity and damage have been developed for use in adults with SLE.³⁰⁻³⁴ These same indices are being used in children. One such tool, the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) has been validated for use in patients with childhood-onset SLE.^{35,36}

The Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) is the only currently available instrument for measuring disease damage in SLE (see Appendix 3).³¹ It was recognised that damage from inflammation cannot be clearly distinguished from damage secondary to medication side effects or other co-morbid conditions; therefore both disease specific and non-disease specific damage are included in the SLICC/ACR DI. It quantifies non-reversible cumulative damage, which has occurred since the onset of the disease. It records damage in twelve organs/systems and has a score range from 0 to 47. Damage is considered non-reversible if any given item was present for at least six months continuously. It is a useful tool for measuring disease damage in adults and children with SLE.³⁷⁻⁴¹

In SLE, there is a bimodal pattern of mortality, either from initial disease activity or from complications relating to either the disease itself or from therapies used in the treatment of the disease.⁴² Renal disease has been shown to be one of the major poor prognostic factors, therefore it is important to identify those at high risk for renal failure and tailor therapy regimens appropriately.²⁴⁻²⁶ Recent improvements in early diagnosis, recognition of milder forms of the disease and improved management strategies are thought to account for the improvement in mortality that has been seen in childhood-onset SLE. In 1981, the five-year survival rate for childhood-onset SLE was reported as 82% but in some more recent studies this figure has increased to 95%.^{25,43,44}

SLE in Sub-Saharan Africa

Childhood-onset SLE in Sub-Saharan Africa has been poorly reported on. It was first described in South Africa by Rovers and Coovadia in 1981 in a case report of three children of Indian descent in Durban.⁴⁵ In 1986 Ransome and Thomson reported on six cases, none in Black African children, from the Gauteng region of South Africa. Renal disease was considered above the other systems as a major influencing system in the morbidity and mortality in childhood-onset SLE and they reported that of the six patients, one patient progressed to end stage renal disease (ESRD) while two had mild renal impairment. Once again, this may just reflect the fact that the clinicians involved were nephrologists.⁴⁶

The first description of childhood-onset SLE in a Black South African child was in 1991. She was a ten year old girl from Durban, who presented with what was described as a fairly typical and full blown picture of SLE. Her main presenting features were renal involvement, haemolytic anaemia and positivity for antinuclear antibodies.⁴⁷

A further study was published in 1994 reporting on the outcome of childhood-onset SLE in Durban. Initially there was a 100% mortality of patients with childhood-onset SLE, but this was improved after changing the management practice in these patients. They concluded that with the judicious use of a few drugs, together with regular and meticulous follow-up, the prognosis of childhood-onset SLE can be greatly improved, even in third world countries.⁴⁸

In 2005, a cohort of 36 patients was reported on in a retrospective analysis from Gauteng, with the main objective of documenting the clinical features and demographics of children with SLE. They concluded that SLE is being increasingly recognized in Black South African children. South African children with SLE present in diverse ways, and the diagnosis is being missed early, therefore patients are presenting late with severe disease.⁴⁹

In 2007, Olowu published two studies, looking at a small number of Black African children in Nigeria. The same eleven children were reported on, firstly describing their initial clinicolaboratory manifestations and short term outcome. They reported both severe renal and extrarenal comorbidities, as well as a high mortality rate in their small cohort. This was thought to be due to a high frequency of delayed and mis-diagnoses. All eleven of these patients had renal disease associated with their SLE, and the second study reported on the renal manifestations and outcomes of these patients. There was a significant association of acute renal failure and tubular dysfunction in this series. This deranged tubular function may be a marker of severe nephritis warranting early confirmatory renal biopsy and aggressive interventional treatment.^{50,51}

In the Western Cape of South Africa there is a large spectrum of ethnicity in the patient population. The patient profile, disease characteristics, morbidity and complications have not been described in the Western Cape, which has a different genetic profile to other parts of South Africa.

Why is Cape Town Different?

South Africa, and Cape Town in particular, has a multi-ethnic population. Genetic studies suggest this group has the highest levels of mixed ancestry in the world, giving the Western Cape of South Africa a unique population mix.⁵²

In South Africa, 'Coloured' people are an ethnic group of mixed race people who possess some sub-Saharan ancestry. The maternal contribution to the Coloured population has been shown to come mostly from the Khoisan population, but it is a mixed race possessing ancestry from Europe, Asia and other southern African countries.^{53,54}

The total number of children under the age of eighteen years old living in South Africa is estimated at about 18,771,000, and it is estimated that around 10% (1,789,000) of these are living in the Western Cape Province, where Cape Town is the main city. There is an almost equal sex incidence (51% males:49% females).⁵⁵

The total population of Cape Town is around 3.5million (B+C), with about 45% of the population being under the age of eighteen years.⁵⁵⁻⁵⁷ The age cut-off for use of Paediatric services in the Western Cape is less than fifteen years old and in 2007, children from 0-to-14 old years made up around 25.8% of the population of Cape Town.⁵⁶

In the whole of South Africa, there are many more Black African children compared to the other racial backgrounds, with around 85% of the total number of children under the age of eighteen years old being Black African. Overall, 8% are Coloured, 5% are Caucasian and 2% are Indian.⁵⁵ This is where Cape Town itself differs from the rest of South Africa. Approximately 35% of the population is Black African, with Coloured people predominating (44%). There is also a much larger proportion of people of Caucasian descent than in other areas of South Africa (19.3%).⁵⁶

Objectives of this literature review

The main objective of this literature review is to try to define the pattern of disease expression in patients with childhood-onset SLE throughout the world, looking specifically at presenting features, disease course, morbidity and mortality. We wanted to look for any major differences in different racial backgrounds to see if this influenced either the presentation or course of the disease.

Methodology

The literature search was performed in PUBMED (www.ncbi.nlm.nih.gov/pubmed/), using the following search strings:

- **SEARCH 1** - SLE + Africa = (SLE[All Fields] AND (“Africa”[MeSH Terms] OR “africa”[All fields]));
- **SEARCH 2** - SLE + characteristics = (SLE[All fields] AND characteristics[All fields]);
- **SEARCH 3** - SLE + clinical features = (SLE[All fields] AND “clinical features”[All fields]);
- **SEARCH 4** - SLE + diagnostic features = (SLE[All fields] AND (“diagnosis”[MeSH Terms] OR “diagnosis”[All fields] OR “diagnostic”[All fields] AND “features”[All fields])).

Results were limited to humans, children less than 18 years old and English language articles. There was some overlap between the searches above, but all article abstracts were obtained and reviewed.

Abstracts dealing with adults only or with the management of SLE only were excluded. All abstracts including patients with neonatal SLE were excluded. Abstracts dealing with drug-induced lupus, mixed connective disease and other rheumatological disease, in particular Juvenile Idiopathic Arthritis, were excluded.

It is well known that SLE is a multisystem disease that can cause severe abnormal outcomes in numerous body systems. According to the ACR diagnostic criteria, as well as outcome score indexes, many systems are commonly affected in SLE.^{20,31,35} Lupus nephritis and neuropsychiatric lupus, in particular, are popular topics in studies.

As this study was an overview of all presenting features, any articles that dealt exclusively with these specific systems were excluded.

Laboratory-based articles that dealt only with biochemical, haematological or immunological results but did not contain enough clinical information were excluded. Articles from the same institutions reporting on a patient cohort that was already included in a larger or more comprehensive study were excluded.

The remaining articles were retrieved and reviewed in full text, and the same criteria applied. Reference lists of all full text articles reviewed were screened for other possible articles. Systematic reviews were not included in the final analysis, but the reference lists were screened for other possible articles. Epub before print reports were reviewed and included where relevant.

The primary aims of the studies varied and were not part of the main inclusion criteria. To be included, all articles had to fulfill the following basic criteria:

- Age cut-offs for ‘children’ clearly defined;
- Patient cohort of more than 30 patients;
- Diagnosis of SLE made on ACR criteria, or if at least four of the criteria was not met, an adequate explanation was given e.g. lupus nephritis on biopsy;
- Basic demographic details given including age and sex – age at either onset of symptoms or diagnosis was required;
- Main clinical features at the time of presentation or diagnosis given.

Retrospective and prospective studies were included, but an accurate description of study methodology was required to allow definition of the study type.

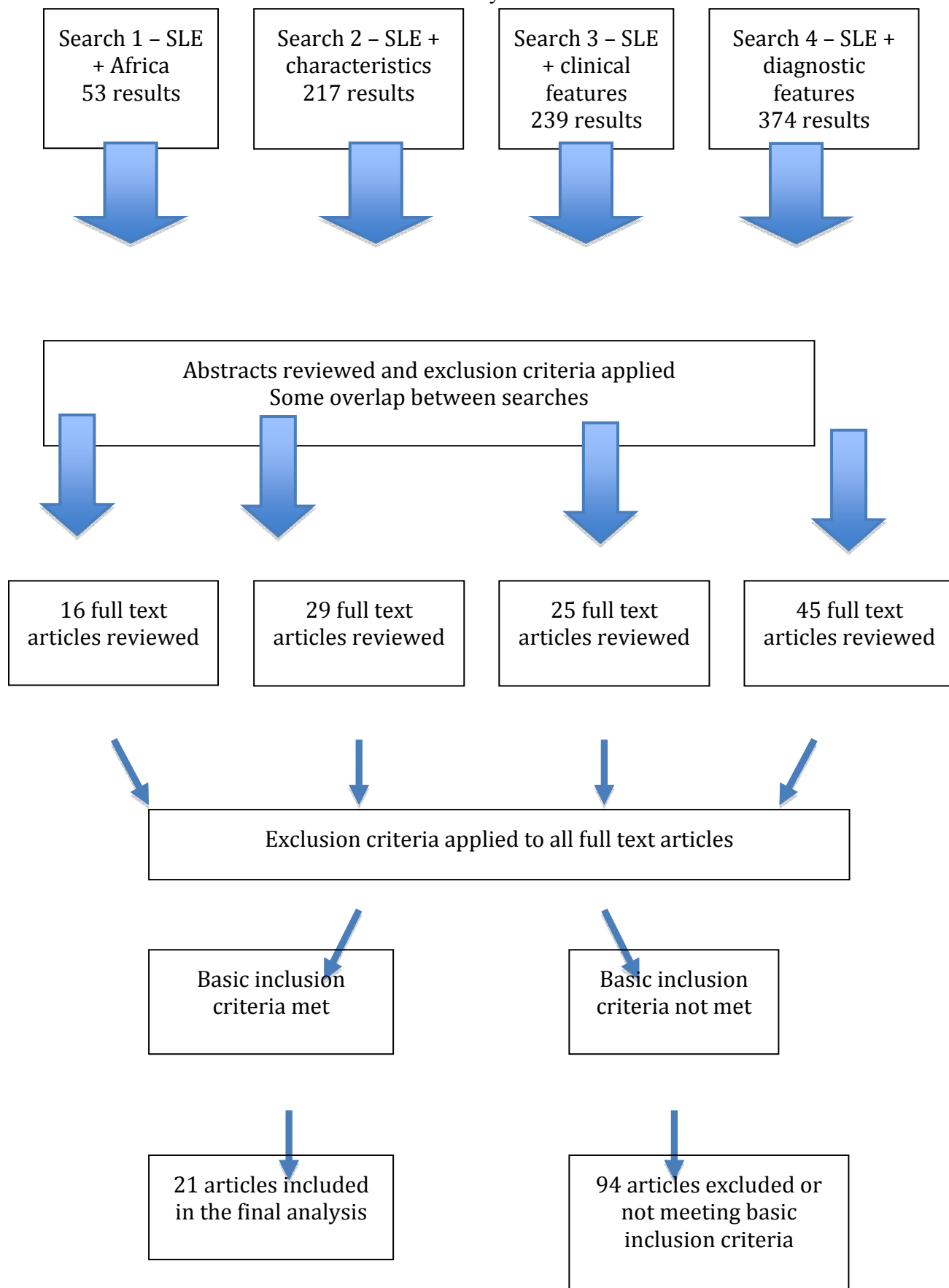
Articles involving both adults and children were included if the information given on the childhood-onset cohort met the above criteria and was described separately. The adult data from these studies was excluded from the analysis.

Outcomes studied in the articles included SLICC/ACR DI scores, mortality and specific renal outcomes. Renal outcomes varied widely between articles, but were included if mortality, number progressing to renal failure or chronic kidney disease, or the number requiring dialysis or a renal transplantation were documented.

It was not possible to do a meta-analysis using the available literature due to different methodology and reporting in the studies.

Results

The search was carried out on the 1st of February 2011.



In summary, the 4 search strings yielded 883 articles. One hundred and fifteen of these articles were reviewed in full text and 21 studies were included in the final analysis.

There were sixteen retrospective studies, two retro- and prospective studies and three prospective studies.

The studies were from many different parts of the world, most commonly from the Middle East, including Egypt in North Africa (n=6) and Europe (n=5). South America (n=4), North America (n=3), the Far East (n=2) and Sub-Saharan Africa and the Indian Subcontinent (n=1) made up the rest of the studies analysed. One of the studies was a direct comparison of African American patients in the United States of America (USA) and Latin American patients in Colombia, South America.

The studies were published from 1981 to 2009, and included data from 1956 to 2006.

All of the studies were conducted in tertiary referral units, with one primarily from a Nephrology unit and eight primarily from Rheumatology/Immunology units. Three studies were from primarily General Paediatric units with three studies also from mixed units incorporating Nephrology, Rheumatology and Haematology departments. There were six multicentre studies.

The age cut offs for the different studies were as follows:

- <14years = 3 studies;
- <15years = 1 study;
- <16years = 7 studies;
- <17years = 5 studies;
- <18years = 5 studies.

Many of the studies had multiple objectives. The main objectives of the studies included in the analysis were:

- Describing demographic, clinical and laboratory/immunological features at presentation, including major organ involvement, and defining pattern of disease expression = 20 studies;
- Morbidity, mortality and survival rate = 2 studies;
- Comparing clinical features in different racial groups = 1 study;
- Clinical and laboratory features at presentation and their association with outcome OR prognostic factors at presentation = 5 studies.

A total of 1996 patients were analysed, 1697 in retrospective or retro- and prospective studies, while 299 were in solely prospective studies.

Overview of results

In all the studies analysed, 371 patients were males, giving a male to female ratio of 1:5.4.

The most reported on clinical features at presentation were renal involvement (n=1996), anti double-stranded DNA (anti dsDNA) antibodies (n=1901), antinuclear antibody (ANA) status (n=1840), central nervous system (CNS) involvement (n=1693) and thrombocytopenia (n=1610).

The commonest clinical presenting features were arthritis in 64.5% (894/1385) and cutaneous features in 62.9% (544/881). Malar rash was present in 58.7% of patients (895/1525), as well as 57.5% of patients (377/656) having some musculoskeletal involvement.

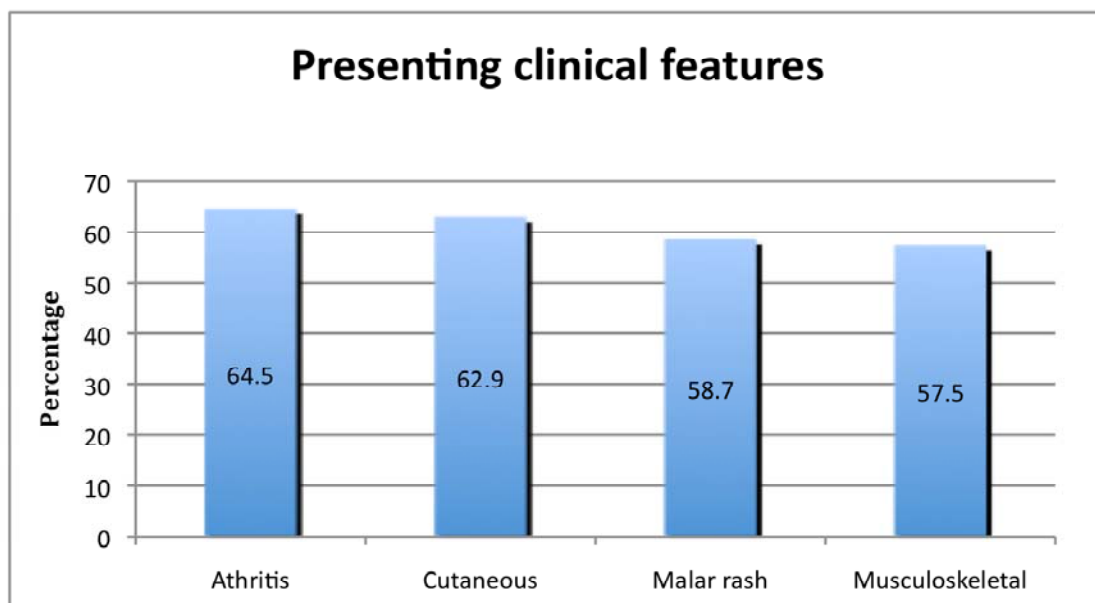


Figure 1. Presenting clinical features

The commonest laboratory findings were a positive ANA in 96.1% of patients (1768/1840), a raised erythrocyte sedimentation rate (ESR) in 91.5% of patients (505/552) and hypocomplementaemia. Studies reported on different complement levels, with 71.8% reporting on a low C3/C4 level (163/227), while 79% reported a low C3 (561/710) and 70.3% reported a low C4 level (499/710).

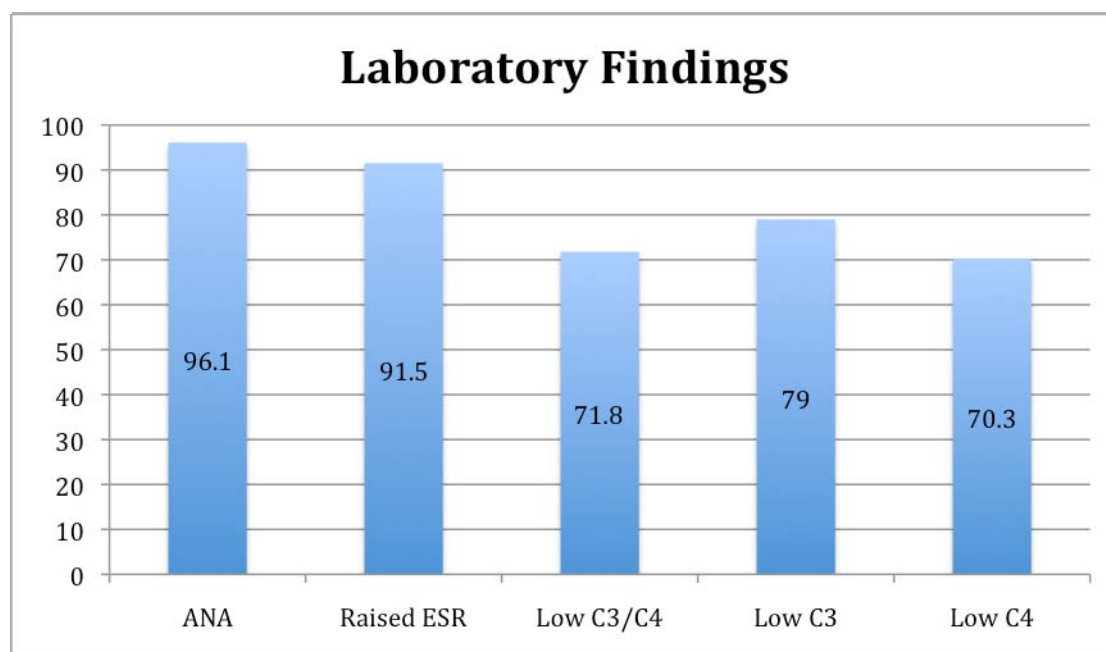


Figure 2. Laboratory findings.

Of all the reporting done, the highest number of patients had positive ANA (1768/1840) and antidsDNA antibodies (1391/1901), malar rash (895/1525), arthritis (894/1385) and renal involvement (917/1996).

Table 1 gives a brief overview of the salient points of all articles involved in this review.

Table 1. Overview of salient points.

Main author; year published; study type	Country; Study dates	Cohort; age range; mean age	M:F	Commonest presenting feature	Other common features
Salah; 2009; Retro ⁵⁸	Egypt; 1990-2005	n = 207; <17yrs; 10yrs	1:2.7	Haem (45%)	Malar rash (38%)
Bakr; 2005; Retro ²⁴	Egypt; 1997-2004	n = 52; <16yrs; 11.9yrs	1:5.3	Renal (81%)	Fever (76%), MSK (65%)
Abdwani; 2008; Retro ⁶	Oman; 1990-2006	n = 50; <14yrs; 8.6yrs	1:5.3	MSK (76%)	Cutaneous (70%), renal (64%), fever (62%).
Moradinejad; 2008; Retro ⁵⁹	Iran; 1996-2006	n = 45; <16yrs; 10.5yrs	1:8	Constitutional (95%)	Arthritis (78%), malar rash (75%)
Uziel; 2007; Retro ⁶⁰	Israel; 1987-2003	n = 102; <18yrs; 13.3yrs	1:4.4	Haem (94%)	Malar rash (49%), anaemia (77%)
Alsaeid; 2004; Pro ⁶¹	Kuwait; 1996-2003	n = 35; <16yrs; 10.7yrs	1:4	Cutaneous (51%)	Arthritis (43%).
Agarwal; 2009; Retro ⁶²	India; 1987-2006	n = 70; <16yrs; 10.5yrs	1:6	Fever (94%)	Renal (77%), MSK (66%)
Wang; 2003; Retro ⁶³	Taiwan; 1980-2001	n = 153; <18yrs; 13.5yrs	1:6	Haem (80%)	Malar rash (77%), renal (59%)
Supavekin; 2005; Retro ¹⁶	Thailand; 1985-2003	n = 101; <15yrs; 9.7yrs	1:6.2	Renal (86%)	Cutaneous (76%), haem (73%)
Iqbal; 1999; Retro ⁶⁴	USA; 1991-1998	n = 39; <18yrs; 12yrs	1:18. 5	MSK (74%)	Cutaneous + anaemia (72%)
Hiraki; 2008; Retro and Pro ⁶⁵	Canada; 1982-2005	n = 256; <18yrs; 13.1yrs	1:4.7	Malar rash + arthritis (61%)	Haem (55%)
Gedalia; 1999; Retro ⁶⁶	USA; 1994-1996	n = 61; <17yrs; 13yrs	1:9.2	Cutaneous (84%)	Arthritis (79%)
	Colombia; 1994-1996	n = 110; <17yrs; 13yrs	1:7.5	Cutaneous (81%)	Arthritis (75%)

Table 1. Continued.

Main author; year published; study type	Country; Study dates	Cohort; age range; mean age	M:F	Commonest presenting feature	Other common features
Appenzellar; 2005; Retro ⁶⁷	Brazil; 1980- 2002	n = 61; <17yrs; 12.1yrs	1:6.5	Arthritis (65%)	Malar rash (58%)
Gonzalez; 2005; Retro ⁴³	Chile; 1984- 2000	n = 50; <16yrs; 10.6yrs	1:3.5	Constitutional (100%)	Arthritis (64%)
Gomez (GLADEL); 2008; Prospective ⁶⁸	South America; 1997-1999	n = 230; <18yrs; 15.3yrs	1:9	Arthritis (83%)	Malar rash (70%)
Bader- Meunier; 2005; Retro ⁶⁹	France; 2002- 2003	n = 155; <16yrs; 11.5yrs	1:4.5	Haem (75%)	Cutaneous (73%), MS (65%)
Rood; 1999; Retro ⁷⁰	Netherlands; 1986-1995	n = 31; <17yrs; 12.3yrs	1:2.4	Anaemia (83%)	Arthritis (74%), thrombocytopenia (72%).
Cervera (Euro-Lupus project); 1993; Retro + Pro ⁸	Europe; 1990-1993	n = 76; <14yrs; 11yrs	1:7	Arthritis (64%)	Malar rash (55%)
Caeiro; 1981; Retro ²⁵	UK; 1956- 1980	n = 42; <17yrs; 13.5yrs	1:7.4	MSK (38%)	Cutaneous (21%)
Font; 1998; Pro ²³	Spain; 1980- 1995	n = 34; <14yrs; 11yrs	1:10	Arthritis (65%)	Malar rash (44%)
Faller; 2005; Retro ⁴⁹	South Africa; 1974-2000	n = 36; <16yrs; 10.9yrs	1:2.6	Cutaneous (77%)	Constitutional (56%)

Pro: prospective; Retro: retrospective; MSK: musculoskeletal; Haem: haematological; CNS: central nervous system; GLADEL: Grupo Latino Americano de Estudio de Lupus.

A summary of the larger studies from different parts of the world is given below.

The Middle East

There were six studies describing features at presentation arising from countries in the Middle East included in this analysis. Although Egypt is an African country, the culture, genetic profile and socioeconomic status is more similar to other countries in the Middle East in comparison to Sub-Saharan African countries.

A total of 491 patients were studied in countries in the Middle East. The male to female ratio was 1:4.1. The commonest presenting features in these patients were fever in 69.6% (71/102), musculoskeletal involvement in 61.4% (153/249) and haematological involvement in 62% (235/379). The most reported on features were renal involvement, CNS involvement and anaemia.

There were two studies describing the demographic data, presentation and clinicolaboratory manifestations of patients with childhood-onset SLE in Egypt. Salah et al studied the largest group in a retrospective folder review of 207 patients.⁵⁸ Some stand out points were a low male to female ratio of 1:2.7 with a relatively low mean age of disease onset of 10 years. Children under five years old made up 4.4% of the cohort. Malar rash (38%) and arthritis (47%) were common presenting features. The kidney was the commonest major organ involved during the course of the disease, especially in male patients, but only 21% of patients had renal involvement at presentation. This figure rose to 67% during the course of the disease.

Comparing this study to Bakr's retrospective study of 52 children, at a dedicated Nephrology unit, suggests a different profile.²⁴ With a mean age of onset of 11.9 years and 17.3% of patients presenting under the age of ten years old, these were only slight differences compared with the difference in the male to female ratio, reported as 1:12 in this group of patients. Interestingly, the most common presenting manifestation was renal disease (80.8%), closely followed by fever (76.6%) and musculoskeletal involvement (65.4%).

The second largest study from the Middle East was done in Israel, looking at 102 patients.⁶⁰ The male to female ratio was 1:4.4, with a later mean age of diagnosis compared to other studies of 13.3 years. Haematological manifestations were the commonest presenting features, present in 94% of patients. With a relatively low amount of renal disease at diagnosis (41%) only a further 12% developed renal disease during the course of the illness. They concluded that with no damage found in 69% of their patients, the outcome was good, which could in fact be due to less CNS involvement than in other cohorts.

Similar studies looking at the demographic data, clinical features and laboratory abnormalities of patients with childhood-onset SLE were conducted in Oman, Iran and Kuwait.^{6,59,61}

The Indian Subcontinent

The only study from the Indian subcontinent that met the inclusion criteria looked at the profile of paediatric SLE in India, retrospectively reporting on 70 patients.⁶² Mean follow up was 18.8 months, but with a range of 1-96 months, some of the follow up was short. The main features at presentation were fever (94.2%), renal (77.1%) and musculoskeletal (65.7%) involvement, as well as a high ESR (98.5%). The overall mortality was 5.7% and renal involvement remained the main cause of morbidity and mortality in childhood-onset SLE in India.

The Far East

Two of the largest studies included in this literature review were retrospective studies carried out in Taiwan and Thailand.^{16,63} A total of 254 patients were studied, with a male to female ratio of 1:6.0. The mean age at diagnosis varied between these two studies, 13.6 years in Taiwanese patients under the age of eighteen years old at presentation compared with 9.7 years in Thailand with an age cut-off of less than

fifteen years old at presentation. The commonest features at presentation were a raised ESR in 90.6% (230/254), low C3 in 89% (226/254) and malar rash in 77.1%(118/153).

In 2003, 153 patients from Taiwan were reported on with the main aim of looking at the morbidity and mortality of patients with childhood-onset SLE, while also discussing the features at presentation.⁶³ Haematological involvement (79.7%), malar rash (77%), and renal disease (58.8%) were the commonest clinical presenting features. Only 4.6% of patients had CNS disease at onset. The study population was looked at as a whole, and then analysed in two different cohorts depending on the year of diagnosis (1980-1990 v 1991-2001). There was a significant reduction between these two groups in infection, skeletal manifestations and end-stage renal disease (ESRD). Overall mortality was 21.6% at five-year follow-up and 28.8% at ten-year follow up. Being male was actually a good prognostic factor, but having ESRD was a poor prognostic factor. Ten-year survival increased from 44% to 77.5%. However, 19% of these patients were lost to follow-up.

A retrospective folder review of 101 patients in a general paediatric unit in Thailand was reported on.¹⁶ The aim was to identify presenting symptoms and signs as well as laboratory and immunological findings. The mean age of diagnosis was low at 9.7 years, with 3% being under the age of five years old and 38.6% being under the age of ten years old at diagnosis. In patients under five years old, the male to female ratio was 1:2, compared to 1:5 in five to ten year olds and 1:8 in ten to fifteen year olds. Renal disease was present in 86.2% of patients at presentation, with only 31.7% having musculoskeletal involvement. Incidences of cardiac, pulmonary, gastrointestinal and musculoskeletal disease were lower, which may be secondary to referral patterns or ethnic diversity. They concluded that age at disease onset, clinical manifestations and laboratory investigations are comparable to other reports.

North America

356 patients in the studies included in the analysis were from countries in North America. With 17.4% of these patients being male, the male to female ratio was 1:5.7. The commonest clinical presenting features in North American studies were cutaneous manifestations (79%), musculoskeletal involvement (74.4%), and arthritis (64.4%). A low C3/C4 was present in 76.9% and 87.2% had a raised ESR.

The largest North American study analysed was conducted in Canada aiming to determine the frequency and characteristics of clinical symptoms and signs, laboratory features and to examine correlations between disease manifestations and disease activity over time.⁶⁵ There was a mean age at diagnosis of 13.1 years with a male to female ratio of 1:4.7. The commonest presenting features were arthritis and malar rash (61%). Renal involvement was present in 37% at disease onset, rising to 55% during the course of the disease. There was a high amount of CNS disease (16%) but most of these patients had headaches, which is not part of the ACR diagnostic classification. There was a low mortality (2.3%) even with a high incidence of major organ involvement.

In Florida in the USA, 39 patients were reported on with one third of these patients being described as having atypical manifestations of the disease.⁶⁴

South America

The South American studies made up 451 of the patients included in the analysis. The commonest clinical features at presentation were constitutional features (100%), cutaneous features (80.9%) and arthritis (76.7%).

Of the studies meeting the inclusion criteria, the largest study found was published by the GLADEL (Grupo Latino Americano de Estudio de Lupus) group who conducted a large multicentre prospective study looking at the clinical characteristics of childhood-

onset SLE in a cohort of patients with mixed ethnicity.⁶⁸ A total of 1214 patient of all ages with SLE were looked at, with 230 of these patients being under the age of eighteen years old at diagnosis. There was a mean age of diagnosis of 15.3 years, with a mean follow up time of 1.7 years (0.8-2.9 years). The male to female ratio was 1:9. Common presenting features were arthritis (83%), malar rash (70.4%) and fever (63.5%). A large proportion were anti-smith (anti-sm) antibody positive (51.3%) with a relatively low amount positive for anti-dsDNA antibodies (67%). Mortality in this group of children was 3.8%. There was less severe renal impairment in children compared with adults, differing from other studies. They concluded that paediatric lupus has a more severe presentation due to higher disease activity indexes, with major haematological, cutaneous and CNS involvement.

Retrospective studies were conducted in Chile and Brazil looking at presenting features of childhood-onset SLE.^{43,67}

Europe

Three hundred and thirty-eight patients were included from studies in European countries. In these studies patients generally had fewer features at presentation than in other areas of the world. Only 61.9% of patients had cutaneous involvement with 48.9% having a malar rash, 15.3% having oral ulcers and 16.9% presenting with alopecia. Of all the areas studied, renal disease was lowest in this group of patients (35.8%). The commonest presenting features in Europe were haematological involvement (74.8%) and arthritis (64.5%).

The oldest study included in this review was a multicentre study in the UK looking at the clinical and laboratory features in 42 patients.²⁵ Some of the follow up was long (mean 7.1 years) with all of the patients being followed-up for at least six months. There was a mean age of diagnosis of 13.5 years, with a male to female ratio of 1:7.4. All of the patients were ANA positive with a high ESR at diagnosis. The commonest presenting features were musculoskeletal (38%) and cutaneous involvement (21%). The mortality was 14.2%, with ESRD, infection and active SLE being the main causes.

The largest European study looked retrospectively at the clinical and laboratory features at presentation of 155 patients in a multicentre French analysis.⁶⁹ A standardised questionnaire was sent to 89 Paediatric centres in France, with a response rate of 73%. The commonest presenting features were haematological (75%), cutaneous (73%) and musculoskeletal (65%) involvement. In a similar conclusion to the study from Florida, one third of the patients had non-classical manifestations of SLE at presentation.⁶⁴

Studies conducted in Spain and the Netherlands reported on smaller cohorts of patients, prospectively and retrospectively respectively.^{23,70}

South Africa

A study of 36 patients in Johannesburg was the only Sub-Saharan study to meet the inclusion criteria of this literature review.⁴⁹ Children under the age of sixteen years old were reported on, with the most striking feature being the low male to female ratio of 1:2.6. The commonest presenting manifestations were cutaneous features (77%), constitutional features (56%) and renal involvement (44.4%). They advised of warning signs at the end of the study so as to help with earlier diagnosis as many of the patients in this population presented with severe disease.

Studies with direct comparisons

The only study included in this analysis directly comparing two different patient populations looked at 61 patients from New Orleans in the USA and 110 patients from Colombia.⁶⁶ A cross sectional, comparative, multicentre and binational retrospective study based in Rheumatology services was carried out.

They aimed to compare clinical and serological features of SLE in African American and Latin American children. Both groups had a mean age of diagnosis of 13 years

old, with the African American children having a higher male to female ratio than the Latin American children (1:9.2 v 1:7.5). The commonest clinical presenting features in African American children were cutaneous involvement (84%) and arthritis (79%). 100% of these patients had a positive ANA and 83% of these patients had hypocomplementaemia. In Latin American children, the commonest clinical presenting features were also cutaneous involvement (81%) and arthritis (75%). Ninety-six percent had a positive ANA. More Latin American patients had a low C3 (86%) and C4 (90%). African American patients had a higher prevalence of discoid lupus and pulmonary fibrosis and a lower prevalence of photosensitivity and livedo reticularis than Latin American patients.

Outcomes

Only five of the studies included in the review reported on the SLICC/ACR DI as an outcome measure for their patients. Reporting methods varied significantly between the studies so it was difficult to do direct comparisons.

All of these studies were published after 2005 apart from one small European study. Three of the five studies had a cohort of more than one hundred patients.

In Canada, 1.7% of patients had disease damage, according to the SLICC/ACR DI, at six months after diagnosis. Overall 34% of all patients in this study scored at least one on the SLICC/ACR DI after a mean follow-up time of 3.5 years. They concluded that the majority of patients had major organ involvement in either renal or CNS systems and development of involvement in these organ systems was associated with higher scores of disease activity at diagnosis as well as a greater frequency of damage. Aside from patients with CNS disease, the nature of disease damage was primarily related to medication use rather than the disease process itself.⁶⁵

The GLADEL group reported briefly on the SLICC/ACR DI scores, saying that the maximum score slightly favoured adults with SLE when compared to childhood-onset disease.⁶⁸

Mean SLICC/ACR DI scores were reported on in Israel, Brazil and the Netherlands. In Israel, 53% of the patients completed at least five years of follow-up. Their mean SLICC/ACR DI score was 0.7 (median 0, range 0-8). There was a significantly greater SLICC/ACR DI score among those patients with renal involvement at diagnosis compared to those without initial renal involvement.⁶⁰ In Brazil, the mean SLICC/ACR DI score was 4.9 and SLICC/ACR DI scores did not independently influence survival in this study.⁶⁷ The maximum SLICC/ACR DI score in the Netherlands was 12, with a mean of 2.6 and median score of 2. Muscular atrophy, seizures, renal disorders and retinal changes were the main contributors to these scores in this group of patients.⁷⁰

Only three of the areas gave information on renal outcomes – the Middle East, North America and South America. Only 5.3% of the patients (39/736) developed chronic kidney disease and 3.7% of the patients (21/565) received dialysis during the study periods.^{60,65,66}

The highest amount of patients with chronic kidney disease was in South America, occurring in 11.8% of patients, with only 2.5% having chronic kidney disease and 2% receiving dialysis in North America.^{65,66}

Overall 12.4% of the patients (92/751) died during the study periods. This was highest in the Far East (28.8%) and lowest in India (5.7%) and the Middle East (6.7%).^{6,24,58,61-63}

Discussion

The frequencies of the different presenting features in childhood-onset SLE differ from country to country and even within the same country. There are many variables hypothesised as to the aetiology of SLE, with genetic, environmental, immunological and infective factors all thought to play a role.¹ Because of this multifactorial aetiology it remains difficult to say whether a specific symptom or sign will occur in any individual or any group of patients.

Comparison of presenting features and outcomes is difficult because of differences in patient populations. Each study population is unique. Patients may be of a different race, may have a different severity of disease and be given different treatment regimens. In spite of these limitations some worthwhile observations can be made.

The methods used to collect the data and statistically analyse it varied between studies. Retrospective review of medical records was the commonest method, with only a few prospective studies meeting the inclusion criteria for this literature review. In basic terms, retrospective studies pose a question and look back, while prospective studies ask a question and look forward. Prospective studies usually have fewer potential sources of bias and confounding than retrospective studies.⁷¹

Not all of the studies used the same definitions for different organ system involvement. A good example of this is the different amount of patients suffering from anaemia as a presenting feature of their SLE. Many of the studies used the ACR diagnostic criteria for haemolytic anaemia, while others used an arbitrary cut-off of under 8g/dl or under 12g/dl as having anaemia at presentation. With discrepancies like this, one will obviously obtain skewed data depending on what definition of 'anaemia' was used. Other examples of this include hypertension as renal disease and headaches as CNS disease, which are not part of the ACR diagnostic criteria for these systems.

Age cut-offs for inclusion in the studies reviewed varied, from less than fourteen years old in some studies to less than eighteen years old in others. There is no clear definition for the age at which SLE becomes adult-onset disease rather than childhood-onset disease, and this, along with the fact that different countries have different ages at which patients are seen by adult physicians or paediatricians, is the reason for varying age cut-offs in the studies. This obviously gives a wide variation in the age of disease onset, male to female ratio and overall presenting features, and means that a meta-analysis or direct comparisons are difficult. Adult-onset disease has been shown to present differently to childhood-onset disease, with more renal, CNS and haematological involvement in particular being seen in younger patients.^{8,21,23,72} It has been seen that more adult females have SLE than adult males, but it is thought that this ratio gets closer together with younger ages of onset. This can be seen in the studies included in the review from South America. In Chile patients under the age of sixteen years old had the lowest mean age at diagnosis (10.6 years) with the closest male to female ratio (1:3.5) in this area.⁴³ In comparison, in Colombia and Brazil patients under seventeen years old had mean ages of onset of 13 years and 12.1 years and male to female ratios of 1:7.5 and 1:6.5 respectively.^{66,67} At the extreme end of South American studies, the large multicentre study by the GLADEL group reported on under eighteen year olds at disease onset, with a mean age of onset of 15.3 years and a male to female ratio of 1:9.⁶⁸

The highest male to female ratio (1:18.5) was in North American patients with an age cut-off of under eighteen years old.⁶⁴ On the other hand, the three lowest male to female ratios were in studies looking at patients less than seventeen and less than sixteen years old. The lowest male to female ratios were 1:2.4 in the Netherlands, 1:2.6 in South Africa and 1:2.7 in Egypt.^{49,58,70} The two studies with a mean age of diagnosis under ten years old were both looking at younger patients, with the age cut offs being under fourteen years and under fifteen years old.^{6,16}

In Thailand, the step-wise progression of increasing male to female ratios with increasing age was also seen, with a male to female ratio of 1:2 in patients under five years old rising to 1:8 in patients between ten and fifteen years old.¹⁶ This progression

supports some role in sex steroids in the aetiology of SLE, with more females being affected the closer to puberty the patients get. However, sex steroids cannot explain how there are a large amount of patients presenting at a young age, some before the age of five years old, supporting the idea of multifactorial aetiology.

Although the diagnosis of SLE for inclusion in studies has been defined by the ACR criteria, it has to be remembered that SLE is a lifelong disease with changing features throughout the course of the disease.^{19,20} Apart from in one study, all of the patients included in the studies analysed met four of the ACR criteria for the diagnosis of SLE at time of enrolment. This one study was included as those not meeting the ACR criteria had the diagnosis confirmed through other areas, for example lupus nephritis on renal biopsy.⁶⁹ It is good that a standard has been set for inclusion in studies to allow standardisation while carrying out research. However, it must be remembered that patients with SLE who do not meet the ACR criteria but have evolving disease are excluded from these studies. This may mean that patients with milder disease at onset and less severe symptoms and organ involvement are excluded from these analyses of presenting features.

In the studies analysed, although renal involvement and central nervous system involvement were the most reported on clinical features at diagnosis, the commonest clinical features at presentation were cutaneous, musculoskeletal and haematological involvement. Not surprisingly, as it is the basis of the pathophysiology of the disease, 96.1% of patients were ANA positive and this was the commonest immunological feature in all studies. On the basis of pathophysiology, it is also not surprising to see a high amount of patients with positive anti-dsDNA antibodies, hypocomplementaemia and a raised ESR at presentation.

Renal and CNS disease is highly reported on because in many studies these two organ systems were classed as major organ involvement if they were involved in the disease process. This is also true for haematological involvement, but this seemed under reported on as many of the studies looked at the specific areas within haematological disease and did not comment on the total number of patients with haematological

involvement at presentation. Anaemia and thrombocytopenia were actually reported on more than the broad category of haematological involvement.

The two largest studies allowing comparison in the same country were from Egypt, where different results were given in patients of the same ethnic background. Both studies aimed to describe the demographic, clinical and laboratory features of patients with childhood-onset SLE. Age at onset was similar between the studies.

Interestingly one patient group was from a Rheumatology setting, while the other was from a Nephrology background. The two initial differences seen were variations in the age at diagnosis (10 years v 11.9 years) and male to female ratio (1:2.7 v 1:12). The two major differences in presenting features were the presence of renal disease at presentation (21% v 81%) and the presence of anaemia (17% v 51%). Also, the mortality in the two groups differed as well (5% v 15%). The only other major difference between these two studies was in patients who were anti-dsDNA positive (66% v 96%).^{24,58} It is hypothesised that renal disease is a major predictor of poor outcome, therefore the higher mortality in patients with more renal disease can be expected.²⁴⁻²⁶ Also anti-dsDNA antibodies are thought to be present in more patients with renal involvement. But the other side of the coin is why are there such huge variations in the presenting features in the same country. These differences are thought to be due mainly to referral bias but it is impossible to rule out if there is just a large variation of disease presentation and disease activity in patients of similar ethnicity.

This difference in the sole Nephrology unit raises the issue of possible referral bias.²⁴ Most of the studies were performed in Rheumatology/Immunology led units or multicentre studies. This can obviously give varying results, as patients with mainly one specific organ system involvement may only be seen by their designated subspecialty without a great deal of multidisciplinary input. In all of the studies reviewed renal disease was present in 45.9% of patients studied. As discussed previously, the only study from a Nephrology unit had 81% renal involvement at presentation. The highest amount of renal involvement at presentation (86%) was in a study from Thailand.¹⁶ Two similar studies done in Rheumatology and Autoimmune units gave

renal involvement in only 20-21% of patients.^{23,67} With only 2% having renal disease, patients from the UK had the lowest amount, but this was also the earliest study included in the review. It is possible that with improvements in knowledge of the disease and investigations, that this number is vastly under representing renal involvement – the first patients were recruited in to this study in 1956.²⁵

It is interesting to see how certain features can be almost identical in some ways but vary in others between different ethnic groups. Comparing two groups of patients, one from Europe and one from South America, gives the perfect example of this. With similar cutaneous features (73% v 81%), discoid rash (7% v 9%), renal involvement (50% v 55%) and musculoskeletal involvement (65% v 75%) you may think that these groups of patients had a similar disease profile. However major differences can be seen in other areas, for example CNS disease (17% v 40%), photosensitivity (13% v 56%) and Raynaud's phenomenon (10% v 30%).^{66,69}

The only study giving direct comparisons between two different patient populations looked at Latin American and African American children. They concluded that inter-ethnic differences in the clinical expression of SLE may be explained by the presence of genetic, socioeconomic and environmental features, and that this study confirms the existence of ethnic differences in clinical and serologic features of SLE in children.⁶⁶

Although studies from many parts of the world were included in this analysis, this is definitely not a worldwide review as many areas of the world were both not represented or under represented. There are no articles reviewed from Australia or from Eastern Europe, and only one each from Sub-Saharan Africa and the Indian Sub-Continent.

South Africa has a vast population mix and has been described as having the highest levels of mixed ancestry in the world. There are however many other areas in the world who also have a mixed genetic background. In particular, both Israel and Latin America have diverse multinational and multiracial populations. In Latin America

there is significant mixing of races within each country and between countries. Israel is also known to have a unique genetic background by virtue of its mixed ethnicity with Jews from various origins and a sizable local non-Jewish population. Comparing presenting features from studies from these areas shows some similarities and some differences. There were similar amounts of renal disease in most of these studies, but wide variations in cutaneous involvement, with only 49% of patients in Israel having a malar rash compared to up to 70% from the GLADEL cohort in South America.^{60,68} CNS involvement was also lower in the Israeli cohort compared with South Africa and some Latin American studies.^{43,49,60,66} It has been hypothesised that these differences may be due to socioeconomic and environmental reasons and these comparisons show that there are wide variations in disease expression of childhood-onset SLE between countries.

Reporting methods of the studies describing SLICC/ACR DI scores varied making it difficult to do any direct comparisons. It can be seen that therapy for the disease causes significant morbidity. This can be seen with cataracts, avascular necrosis and muscular atrophy being common indices scored, with these factors being common side effects of corticosteroid use.^{65,70} Renal disease remains a prevalent factor in the SLICC/ACR DI scores. More studies are needed with similar reporting so as to allow accurate comparison of results between study groups, and therefore different countries and ethnicities.

Mortality varied between countries with some of the studies reporting high mortality rates: e.g. 15% in Egypt, 21.6% and 28.8% in Taiwan and 22% in Brazil.^{24,63,67} In Taiwan, two different cohorts were looked at depending on their year of diagnosis. They concluded that ten-year survival probabilities increased significantly from 44.4% in the 1980-to-1990 cohort to 77.5% in the 1991-to-2001 cohort. This indicates a decreasing mortality rate. It has been hypothesised that earlier diagnosis and better medical care may contribute to these improvements. Interestingly, of the four studies with the highest mortality rates, three of them were recruiting patients in the 1980's or earlier.^{25,63,67} The more recent study with a high mortality rate had one of the highest number of patients with renal involvement at presentation. It has been shown that

renal disease at presentation can lead to worse outcomes, so maybe this could be expected.²⁴ Most of the studies used in the analysis from Europe and North America did not report on mortality, so it was difficult to compare rates in developed and developing countries. In Oman and South America the mortality was 4% in each study.^{6,68}

Conclusion

The presenting features of childhood-onset SLE vary from country to country and from studies from within the same country, with large discrepancies because of age cut-offs and subspecialties involved in the studies. Direct comparisons are difficult because of differences in patient populations.

An overview of the current literature has been presented here, highlighting the commonest presenting features of childhood-onset SLE i.e. arthritis, malar rash and other cutaneous features. The commonest laboratory features were a positive ANA result, a raised ESR and hypocomplementemia.

Direct comparison of outcomes between different countries and different ethnic groups was difficult. In general, survival does seem to be improving over the last twenty years. However, there still needs to be a continued drive to identify which patients are more at risk of severe disease, and therefore require more intense therapy, so as to try to limit the side effects of the therapy used while minimising damage from the disease process.

While there are some common features in most of the studies, there is a wide variation of both major and minor organ involvement at presentation.

Although many methodological differences could be cited for the variation in results including different ages, different races and different study design, the results do suggest that childhood-onset SLE has a wide variation in presenting features.

Further reports with large cohorts are needed to allow further comparisons. More prospective studies would be useful to follow the disease process and to look at factors at presentation that may directly affect patient outcomes.

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Part C - Original Article

Title

Characteristics of childhood-onset systemic lupus erythematosus in Cape Town, South Africa.

Journal

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Author

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Conflict of interest

None declared

Abstract

Objectives: To describe the presenting features and disease characteristics of childhood-onset systemic lupus erythematosus including treatment practices and outcomes, looking at those children with renal involvement in greater detail.

Methods: A retrospective folder review was conducted in children diagnosed with systemic lupus erythematosus presenting to the renal or rheumatology services of Red Cross War Memorial Hospital and Groote Schuur Hospital in Cape Town, South Africa between 1998 and 2009. Clinical and laboratory manifestations at presentation as well as the course of the disease and outcomes were studied.

Results: Thirty-two children met our inclusion criteria for the study. The median age of presentation was 10 years (range 2.0-14.8 years). Only four of the patients were male, giving a male to female ratio of 1:7.

The most common initial manifestations were renal (59.4%), arthritis (53.1%) and malar rash (50%). Haematological involvement occurred in almost half of the patients (46.9%). Constitutional symptoms were common in particular lymphadenopathy, weight loss, fever and lethargy. Almost 90% of patients presented with involvement of either the renal, neurological or haematological systems, or a combination of these systems.

Sixty-five percent of patients had a raised erythrocyte sedimentation rate, with 62.5% presenting with a low C3 level and 47% presenting with a low C4.

Antinuclear antibodies, anti-double stranded DNA antibodies, anti-smith antibodies and anti-cardiolipin antibodies were positive in 97%, 75%, 31% and 31%, respectively. There was a statistically significant association between having renal disease and a positive anti-cardiolipin antibody at presentation (p value = 0.0237).

Nineteen patients presented with renal disease and 17 of these had a renal biopsy. Renal disease was more likely to be a presenting feature in younger patients (Risk ratio 1.93; CI 1.34-2.77). The majority of patients (59%) had grade IV lupus nephritis.

During the course of the follow-up a total of 21 patients had renal involvement. Seven of these required dialysis and five received renal transplantation.

The median Systemic Lupus International Collaborative Clinics/American College of Rheumatology damage index score was 1 (range 0-6). Thirteen patients (42%) had no reported long-term damage according to the SLICC/ACR DI.

The overall mortality rate was 6.3%.

Conclusion: Childhood-onset systemic lupus erythematosus is a complex disease presenting in varying ways throughout the world. In Cape Town, a large proportion of patients are presenting with severe disease, most likely presenting late in the disease process. In southern Africa, greater awareness is needed of this complex disease and its severe initial manifestations.

Keywords

Systemic lupus erythematosus, SLE, Africa, childhood, lupus nephritis.

Introduction

Systemic Lupus Erythematosus (SLE) is a multisystem, inflammatory, autoimmune disease that is characterised by the formation of antinuclear antibodies. The aetiology remains poorly understood, however environmental, genetic, immunological and infective factors are all thought to play a role in the pathogenesis.¹

SLE makes up around 4% of all rheumatological disease and although more commonly presenting in adulthood, approximately 15-20% of SLE occurs before the age of 19 years.¹⁻⁴

There is a wide variability in disease presentation and course. It is known that SLE presents differently, not only in respect to age, but also depending on the ethnic background and gender of the patient.⁵⁻⁸ The disease appears to be more common in Europe, Asia and the Americas than in Africa, but much higher in patients of African ancestry living in the United States, United Kingdom (UK) or the Caribbean Islands.⁹⁻¹¹ There is a growing recognition that the perceived low prevalence of lupus in Africa is a reflection of under-diagnosis and poor access to healthcare.¹² There is a female preponderance, but this is also known to vary according to age.^{4,5,13,14} SLE presenting in childhood often involves vital organs and renal disease secondary to SLE can occur. This renal involvement contributes significantly to the long-term morbidity and mortality in children with SLE.^{4,15-17}

Paediatric SLE in Africa

Since SLE was first described in a South African child in 1981, reports of SLE in African children have been rare.¹⁸⁻²² There have only been a few case reports from Sub-Saharan Africa and one retrospective study looking at childhood-onset SLE in South Africa. In 2005, this study, published from the Gauteng region of South Africa, concluded that SLE is being increasingly recognized in black South African children and those South African children with SLE present in diverse ways, with the diagnosis being missed early. Therefore patients are presenting late with severe disease.²²

The prevalence of SLE in adult Black South Africans has been estimated to be 12.2/100,000 although there are no accurate figures available for children in Southern Africa.^{23,24} It has been reported that SLE in indigent adult South Africans carries a poor prognosis, with nephritis being common and the only independent predictor of poor outcome.²³

South Africa, and Cape Town in particular, has a multi-ethnic population. Genetic studies suggest this group has the highest levels of mixed ancestry in the world, giving the Western Cape of South Africa a unique population mix.²⁵⁻²⁷

As there is a paucity of data on childhood-onset SLE in South Africa, this retrospective study was aimed to describe the disease characteristics at presentation, disease activity, treatment practices and outcomes in our cohort of patients with childhood-onset SLE from Cape Town, South Africa. With renal involvement being hypothesised as being a major influence on outcome, this study also looks specifically at the patients with renal disease associated with their SLE in more detail.

Methodology

A folder review of all patients diagnosed with childhood-onset SLE at the Red Cross War Memorial Children's Hospital and Groote Schuur Hospital was performed. These patients were seen in both Rheumatology and Nephrology clinics at these tertiary institutes between 1998 and 2009.

The patient folders were evaluated retrospectively using clinical notes and by review of an electronic results database, via the National Health Laboratory Service (NHLS), by the two main authors. The notes were cross-evaluated by the second reviewer to ensure all appropriate data was collected.

The following factors were looked at:

- Demographics – including age, sex and racial background;
- Date of presentation, date of diagnosis of SLE, date of last clinical visit to hospital;
- Presenting features of the disease – classified according to the American College of Rheumatology (ACR) Classification Criteria for SLE;^{28,29}
- Other common features at presentation not specifically included in the ACR criteria;
- Affected systems throughout the course of the disease;
- Any documentation of serious infection requiring hospitalization.

From the above data, age at presentation and length of follow up was calculated.

The racial/ethnic background was divided in to 3 different categories and classification was done according to self-reporting by the patients themselves:

- Caucasian;
- Black African;
- Coloured.

Laboratory abnormalities at the time of presentation to our referral hospitals were recorded including full blood count (FBC), erythrocyte sedimentation rate (ESR), serum creatinine levels, complement levels (C3 and C4), urinalysis and serologies including titres of antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies and anticardiolipin antibodies (ACLA). The glomerular filtration rate (GFR) was calculated using the modified Schwartz formula:

$$\text{Estimated GFR (eGFR)} = (k * \text{height in cm}) / \text{serum creatinine (in mg/dL)}^{30}$$

[* = k is a constant that depends on muscle mass, which itself varies with a child's age]

Renal biopsies performed at any time during the course of the illness were reviewed by a Consultant Pathologist and were all classified according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification for lupus nephritis (LN).^{31,32}

The Systemic Lupus Erythematosus International Collaborative Clinics/American College of Rheumatology damage index (SLICC/ACR DI) was used as an outcome parameter for prognosis.³³ This was recorded at the time of their most recent visit to the hospital. The specific categories related to scores were recorded.

The therapy that the patient received at any time during the course of the disease was recorded.

Antibody testing

Antibody testing was performed by the National Health Laboratory Service of South Africa. The following antibody tests were performed using Fluoroenzymeimmunoassay on the instrument ImmunoCAP 100 (Phadia, Uppsala, Sweden):

- ANA – EliA Symphony for the in vitro qualitative measurement of antinuclear IgG antibodies in human serum. Used together with EliA IgG method;
- Anti-dsDNA antibodies – EliA dsDNA for in vitro qualitative measurement of IgG antibodies directed to dsDNA in human serum and plasma;
- Anti-smith (anti-Sm) antibodies – EliA Sm for the in vitro quantitative measurement of IgG antibodies directed to Sm in human serum;
- ACLA – EliA Cardiolipin IgG for the in vitro quantitative measurement of IgG antibodies directed to cardiolipin in the serum.

Definitions

Serious infection

Serious infections were defined as a positive blood culture and/or evidence of raised infective markers with admission to hospital requiring at least seven days of intravenous antibiotics.

Ethnicity

In South Africa, ‘Coloured’ people are an ethnic group of mixed race people who possess some sub-Saharan ancestry. The maternal contribution to the Coloured population has been shown to come mostly from the Khoisan population, but it is a mixed race possessing ancestry from Europe, Asia and other southern African countries.^{26,27}

Major Organ Involvement At Presentation

Major organ involvement was defined as the presence of, or combination of, renal, neurological or haematological involvement at presentation.

Hypertension

Defined as an average systolic and or diastolic blood pressure that was greater than or equal to the 95th percentile for sex, age and height on 3 or more occasions.³⁴

SLICC/ACR DI score

The SLICC/ACR DI is the only currently available instrument for measuring disease damage in SLE.³³ It was recognised that damage from inflammation cannot be clearly distinguished from damage secondary to medication side effect's or other co-morbid conditions, therefore both disease specific and non-disease specific damage are included in the SLICC/ACR DI. It quantifies non-reversible cumulative damage, which has occurred since the onset of the disease. It records damage in 12 organs/systems and has a score range of 0-47. Damage is considered non-reversible if any given item was present for at least six months continuously. It is a validated tool for measuring disease damage in adults and children with SLE.³⁵⁻³⁹

Statistical analysis

STATA 11.1 was used for statistical analysis. The Shapiro-Wilks test was used for data distribution. All data was found to be non-parametric. Expected frequencies were calculated and as some frequencies were less than 5, the two-tailed Fisher's exact test was used to calculate p values. A p value of <0.05 was considered statistically significant.

Results

A total of 37 children had a diagnosis of SLE. Patients with insufficient diagnostic features (two or less of the ACR criteria) were excluded. Patients with only three of the ACR criteria were studied in more detail to confirm or refute the diagnosis. There were three patients with fewer than four ACR criteria who were included in the analysis:

- Patient 1 – hepatitis, arthritis, ANA positive and anti-Sm antibody positive – included due to high specificity of Anti-Sm antibody;
- Patient 2 – class IV lupus nephritis, ANA positive and anti-Sm antibody positive – included due to confirmed lupus nephritis;
- Patient 3 – cutaneous vasculitis, pulmonary disease, ANA positive, arthritis – included as patient developed lupus nephritis during the course of follow-up.

The total number of patients included in the study was 32. All patients had a follow up time of at least 6 months, with the average duration of follow up being 5.6 years (range 0.5 – 17 years).

There were 4 male patients and 28 female patients giving a male-to-female ratio (M:F) of 1:7. The median age of presentation with the disease was 10 years (range 2.0 – 14.8 years). Four of the patients (12.5%) were under 6 years old at presentation, with 12 patients (37.5%) presenting before their 10th birthday.

The breakdown of ethnic background is outlined here:

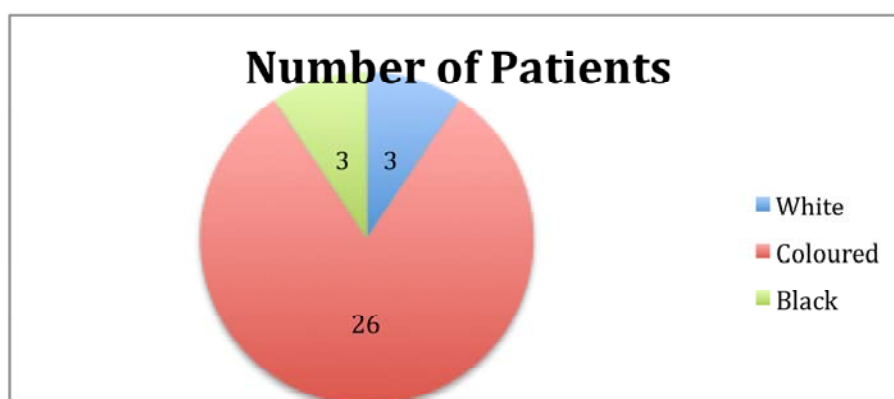


Figure 1. Breakdown of ethnic background

The commonest clinical presenting feature at presentation was renal disease (59.4%), closely followed by arthritis (53.1%) and malar rash (50%). Constitutional symptoms were present in most patients at the time of presentation, with the breakdown of some of the more common features shown in table 1.

Table 1. Clinical presenting manifestations.

Features	Patients (n=32)	Percentage (%)
Female	28	87.5%
Under 6 years old at presentation	4	12.5%
Under 10 years old at presentation	12	37.5%
Renal involvement ^a	19	59.4%
Arthritis ^a	17	53.1%
Malar rash	16	50%
Haematological involvement ^a	15	46.9%
Central nervous system (CNS) involvement ^a	2	6.3%
Photosensitivity	7	21.9%
Oral ulcers	8	25%
Serositis	8	25%
Hypertension ^b	7	21.9%
Lymphadenopathy	11	34.4%
Loss of weight	10	31.3%
Lethargy	10	31.3%
Fever	10	31.3%
Headaches	6	18.8%
Raynaud's phenomenon	4	12.5%

^a = as per ACR criteria^{28,29}

^b = as per hypertension definition³⁴

Twenty-eight of the patients had involvement of the renal, neurological or haematological systems, or a combination of the above systems, at presentation. Therefore 87.5% of the patients had major organ involvement at presentation.

The breakdown of laboratory results at presentation is shown in table 2, with a comparison made between renal and non-renal patients.

Table 2. Laboratory results.

	ALL PATIENTS (n=32)		RENAL PATIENTS (n = 19)		NON-RENAL PATIENTS (n=13)	
ANA +ve	31	96.9%	19	100%	12	92.3%
Anti-dsDNA +ve	24	75%	15	78.9%	9	69.2%
Anti-Sm +ve	10	31.3%	5	26.3%	5	38.4
ACLA +ve	10	31.3%	9	47.4%	1	7.7%
False +ve syphilis	0	0%	0	0%	0	0%
Low C3	20	62.5%	14	73.7%	6	31.6%
Low C4	15	46.9%	9	47.4%	6	31.6%
ESR >20	21	65.6%	10	52.6%	11	84.6%
Hb <10	10	31.3%	6	31.6%	4	30.8%
Platelets <150	6	18.8%	4	21.2%	2	15.4%

ANA: antinuclear antibody; Anti-dsDNA: anti-double-stranded DNA; Anti-Sm: anti-smith; ACLA: anti-cardiolipin antibody; C3: complement component 3; C4: complement component 4; ESR: erythrocyte sedimentation rate; Hb: haemoglobin.

Comparisons of presenting features from other studies of childhood-onset SLE from around the world are shown in table 3.

Table 3. Comparisons from other areas around the world.

	Cape Town	South Africa Faller ²²	Egypt Salah ⁴⁰	Israel Uziel ⁴¹	Thailand Supavekin ¹⁴	USA Gedalia ⁴²	Colo- mbia	South America Gomez ⁴³	France Bader- Meunier ⁴⁴
Cohort	32	36	207	102	101	61	110	230	155
M:F	1:7	1:2.6	1:2.7	1:4.4	1:6.2	1:9.2	1:7.5	1:9	1:4.5
Median age	10				10				12
Mean age		10.9	10	13.3		13	13	15.3	
Renal (%)	59.4	44.4	21	41	86	44	55	49	50
Arthritis (%)	53.1	39	47	-	-	79	75	83	-
Malar rash (%)	50	47	38	49	53.5	69	52	70	39
Haem (%)	46.9	-	45	94	73	-	-	-	75
CNS (%)	6.3	19	7	7	21	31	40	-	17
ANA (%)	96.9	-	95	93	96	100	96	97	97

Haem: haematological; CNS: central nervous system; ANA: antinuclear antibody

Table 4 shows the illnesses and systems that were affected throughout the follow up but were not present at the time of presentation.

Table 4. Illnesses and systems affected during follow-up.

Feature	Patients (n=32)	Percentage (%)
Pulmonary Tuberculosis	4	12.5%
Pleural effusion	5	15.6%
Pneumonia	4	12.5%
Other respiratory	5	15.6%
CNS	10	31.3%
Cardiovascular	2	6.3%
Gastrointestinal	5	15.6%
Musculoskeletal	5	15.6%
Skin	12	37.5%
Eyes	5	15.6%
Haematology	6	18.8%
Renal	2	6.3%

CNS: central nervous system.

Twelve of the patients suffered from serious infection during the course of the illness, suffering a total of 18 serious infections between them. Three patients had multiple episodes of serious infection.

Renal Patients

Of the 32 patients with SLE in this study, 19 had confirmed renal disease, as per the ACR criteria, at presentation. Seventeen of these patients (89.5%) had proteinuria of more than 0.5g/day and 15 (78.9%) had cellular casts seen on urine at presentation. Renal disease was more likely to be a presenting feature in younger patients (Risk ratio 1.93; CI 1.34-2.77).

The eGFR was calculated for all patients presenting with renal disease and these were classified using the Kidney Disease Outcome Quality Initiative (KDOQI) classification of Chronic Kidney Disease (see table 5):⁴⁵

Table 5. Estimated GFR and scoring according to KDOQI classification.

STAGE	GFR	DISEASE	NUMBER (n=19)	%
1	>89	Kidney damage with normal or increased GFR	6	31.6%
2	60-89	Kidney damage with mildly reduced GFR	6	31.6%
3	30-59	Moderately reduced GFR	1	5.3%
4	15-29	Severe reduction in GFR	1	5.3%
5	<15 or dialysis	Kidney failure	5	26.3%

GFR: glomerular filtration rate.

Seventeen out of these 19 patients with renal disease had a renal biopsy performed during the course of their illness. The LN was graded accordingly:^{31,32}

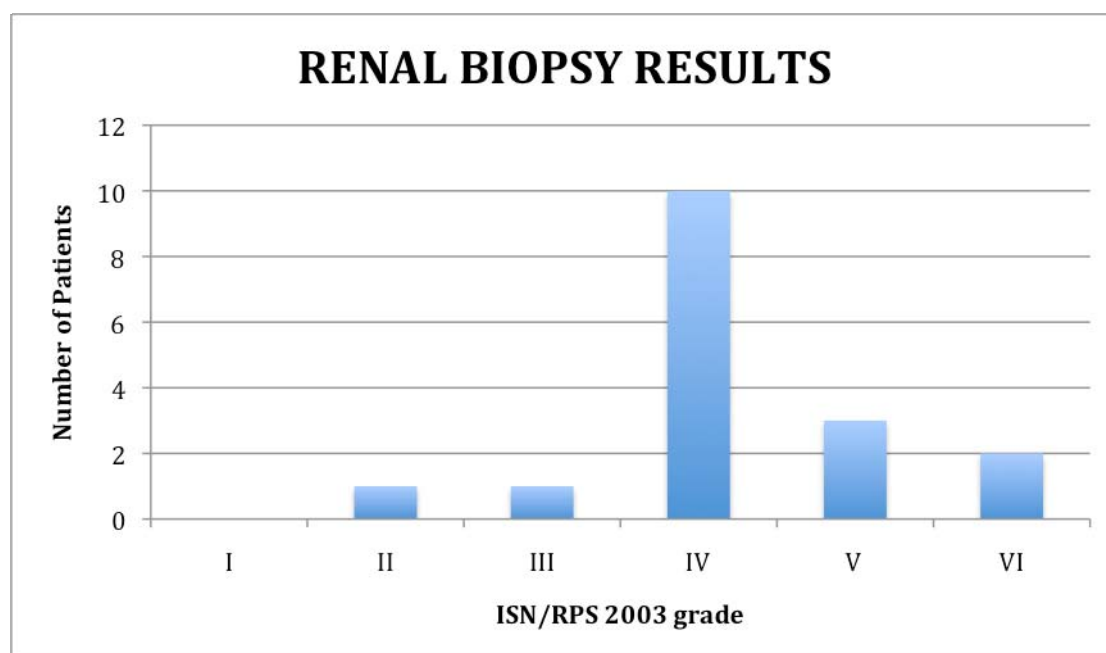


Figure 2. Renal biopsy results

Associations were looked at of different presenting features giving an increased risk of renal disease at presentation. There was a statistically significant association between having renal disease and a positive ACLA at presentation. Table 6 shows these associations and their respective p values.

TABLE 6. Associations with renal disease.

FEATURE AT PRESENTATION	P VALUE FOR ASSOCIATION WITH RENAL DISEASE
Age <6 years old vs age >6 years old	0.0641
Age <10 years old vs age >10 years old	0.7128
Anti-dsDNA positive vs anti-dsDNA negative	0.6838
ACLA positive vs ACLA negative	0.0237
Anti-Sm positive vs anti-Sm negative	0.6993
Low C3 or C4 vs normal C3 and C4	0.4181
ESR >20 vs ESR <20	0.229

Anti-dsDNA: anti-double-stranded DNA; ACLA: anticardiolipin antibody; Anti-Sm: anti-smith; C3: complement component 3; C4: complement component 4; ESR: erythrocyte sedimentation rate.

Treatment

The disease modifying treatment given at any time during the course of the illness is shown in table 7.

Table 7. Treatment given during course of illness.

DRUG	NUMBER (n=32)	PERCENTAGE (%)
Oral corticosteroid	32	100%
Azathioprine	21	65.6%
Chloroquine	21	65.6%
Mycophenolate mofetil	12	37.5%
Methotrexate	10	31.3%
Cyclophosphamide	14	43.8%
Intravenous Immunoglobulin	3	9.4%
Rituximab	1	3.1%

Outcome

The breakdown of the SLICC/ACR DI scores is as follows (one patient had inadequate clinical notes to do an accurate score):

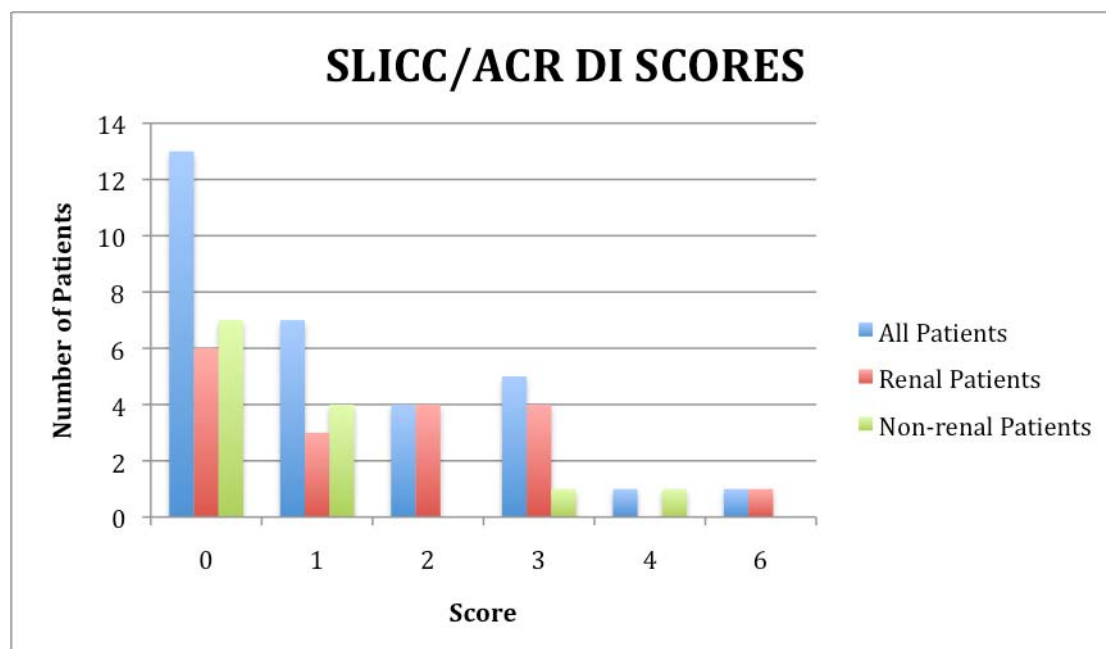


Figure 3. Breakdown of SLICC/ACR DI scores.

The median SLICC/ACR DI score after follow-up was 1, ranging from 0 to 6. Thirteen patients (42%) had no reported long-term damage according to the SLICC/ACR DI.

Renal involvement was the commonest system to be scored in the SLICC/ACR DI (6 patients), followed by pulmonary (4 patients) and musculoskeletal (4 patients) involvement.

Dialysis and transplant

During the course of their follow up in this study, a total of 21 patients had renal involvement - two patients developed it during the course of the disease. Of these, seven required dialysis and five received renal transplantation.

Mortality

Two patients died, giving an overall mortality of 6.3%. One patient died in 2006 due to end stage renal disease (ESRD) while the other died more recently in 2010 from extensively drug-resistant tuberculosis.

Discussion

The objective of this study was to determine the clinical presentation, treatment practices and outcomes of childhood-onset SLE in a South African population that has never before been reported on.

Despite the many published cases of childhood-onset SLE, its true incidence and prevalence is unknown. One of the main reasons for this is that there is not a strict definition of childhood-onset SLE. The most frequent cut-off ages are 14 or 16 years old at onset of the disease. However, several studies use a higher or lower cut-off age. In our study we used a cut off of 16 years because over this age patients are referred to the adult services in our area.

Comparison of outcomes with other studies is difficult because of differences in patient populations. Each study population is unique. Patients may be of a different race, may have a different severity of disease and be given different treatment regimes. In spite of this limitation, certain comparisons have been made in this study.

Ethnicity

There are numerous different racial backgrounds in our study population, defined as Black African, White and Coloured. Genetic studies suggest that our cohort has one of the highest levels of mixed ancestry in the world, giving the Western Cape of South Africa a unique population mix.²⁵⁻²⁷ There have been many reports from all over the world, but with most of the patients in this study group being from the Coloured population, this study population is of unique ethnicity which has never before been reported on.

Male to female ratio with age

In childhood-onset disease, a progression of increasing male to female ratios occurring with increasing age has been reported.¹⁴ Our study also showed this progression, with a male to female ratio of 1:3 for six to ten year old children and 1:9 for children presenting after their tenth birthday.

Our overall male to female ratio was 1:7. Some other studies from Africa have shown a much lower male to female ratio; 1:2.6 in South Africa and 1:2.7 in Egypt.^{22,40} However in North America (1:18.5) and Europe (1:10), as well as in another study from Egypt (1:12), higher ratios, similar to that seen in adults, have been reported.^{15,46,47}

Our patients had a median age of 10 years, which was similar to a much larger study from Thailand, which also had a median age of 10 years and a similar male to female ratio of 1:6.2.¹⁴ However, around the world the age at onset and female preponderance in childhood-onset SLE varies considerably.

Major organ involvement at presentation

Major organ involvement at presentation has been reported to be a major influencing factor on the long-term prognosis of patients with childhood-onset SLE.^{3,16,48} Almost 90% of our patients presented with major organ involvement, agreeing with the previous view that children, unlike adults, commonly present with major organ involvement.^{4,47,49,50}

The fact that most of our patients presented with major organ involvement at presentation supports the conclusion from Faller et al that patients in South Africa present late with severe disease at presentation.²² Despite this our patients had relatively good outcomes in terms of SLICC/ACR DI scores and mortality. The correlation of major organ involvement at presentation and poor outcome was not shown in this cohort of modest size. It must be remembered, however, that mild cases may not be included in this analysis as they may remain unreported due to them not being referred to the tertiary institute for further evaluation.

Different presenting features and comparison

There is a wide variation among different studies in the prevalence of manifestations of childhood-onset SLE. This may be due to differences in the genetic make up of patients who come from various ethnic backgrounds, age at presentation, or from referral bias. The most frequent findings in this population at presentation were renal involvement, arthritis, malar rash and haematological involvement. Renal disease was

also the highest prevalent factor in another South African study, although at lower levels (44%).²² Also, up to 58% of their patients had developed renal disease by the end of the their follow up time, compared to 66% of our patients. On the other hand, they reported much higher CNS involvement at presentation (6.3 vs 19%), which is similar to that reported in France and Thailand.^{14,44} Our relatively lower incidence of CNS involvement is similar to Northern African areas as well as other areas of mixed ethnicity.^{15,40,41,51} There were hugely varying reporting of haematological involvement at presentation, ranging from 45% in Egypt and 47% in our study, to as high as 94% in Israel.^{40,41} One possible explanation for this is the specific definition used for haematological involvement, although the Israeli study also used the ACR diagnostic criteria for haematological involvement.⁴¹

With renal involvement, arthritis and malar rash being the commonest presenting features, this is similar to Colombian children.⁴² However, they had a much higher amount of photosensitivity and Raynaud's than our patients. The fact that this was a retrospective study means that these features, most often elicited in history, may not have been consistently well documented.

Although the presenting features of childhood-onset SLE in our diverse population group was similar to other countries throughout the world, some key differences can be seen, and no common thread can be clearly identified.

Laboratory results

Most large series of childhood-onset SLE included a variable number of patients with SLE who were ANA negative at presentation, usually 3-5%.^{40,43,44,52} This can also be seen in our patients, where all bar one were ANA positive at time of presentation.

Anti-dsDNA antibodies have been reported to be positive in 85-95% of patients, but this is lower in our study (75%). One reason could be improving laboratory techniques to diagnose this autoantibody positivity. In this small cohort of African children, ACLA positivity at presentation was helpful as a diagnostic aid associated with the presence of renal involvement.

The presence of anti-Sm antibodies is a very specific, but not sensitive test for the diagnosis of SLE.⁵³ In our study, we found only 31% of patients with anti-Sm antibodies, which is lower than North America but similar to two European studies.^{7,42,44,46,54,55}

Infections

It has been shown that patients with SLE have a greater susceptibility to infections and that this is a leading cause of mortality in this group of patients.^{16,56-58} The increased frequency of serious infection observed in this study most probably results from the combined effect of the disease itself and the use of immunosuppressive therapy. Although 37.5% of our patients had a serious infection at some point during their follow up, only one of the patients died from an infective cause. In our patient population there is a high prevalence of TB and it can be seen that 12.5% of our patients developed TB during the follow-up period. This is an added complication to deciding treatment regimens, ensuring we maximise treatment while limiting immunosuppression and other potentially serious side effects.

Renal Patients

Lupus nephritis (LN) is considered to be more frequent and more severe in children than adults.⁴ The incidence of LN in the present study was 59.4%, which is comparable to another study carried out in a mixed Nephrology/Rheumatology unit.⁵⁹ However, it is lower than some other African countries as well as in Thailand, but much higher than the reported 20-21% in another Egyptian study, as well as in Europe and South America.^{14,15,40,47,51} Hypotheses for these differences could be referral bias and the different specialties looking after the patients. There seemed to be varying incidences of renal involvement depending on whether the studies were conducted in Nephrology, Rheumatology, or mixed Nephrology/Rheumatology units.

There was an increased risk of developing LN with younger age at onset and, with renal disease being a major factor in morbidity and mortality, this supports the hypothesis of childhood-onset disease in South Africa presenting late in the disease process, especially in patients under the age of 6 years old.

Biopsies. As we used the newer ISN/RPS classification for renal biopsies in LN, there were limited direct comparisons to make between our study and other, larger reports. However, it can easily be seen that this study confirms the severity of the initial renal disease in childhood-onset SLE patients, with class IV LN occurring in over 50% of those biopsied. This high incidence of Class IV disease is similar to many studies throughout the world.⁶⁰⁻⁶³ Class IV LN is defined as diffuse LN in both the newer ISN/RPS classification as well as the older WHO classification of LN.^{31,32,64,65}

Chronic Kidney Disease. Our patients with renal disease seemed to fall in to 2 main categories. Using the KDOQI classification of Chronic Kidney Disease, the majority (63.2%) had mild kidney damage or kidney damage with normal renal function. On the other hand, just over a quarter of patients (26.3%) had kidney failure at presentation.

ESRD has been reported to be 10% in African Americans and 12% in Latin Americans.⁴² These values are obviously lower than our reported 26.3% of patients having ESRD, supporting the hypothesis of our cohort of patients presenting with more severe disease than in other areas throughout the world.

Pharmacological treatment

The management of SLE and LN is very difficult. As there is no single aetiology, there is no single cure to the disease. The aim of therapy at all stages of childhood-onset SLE is to maximise the therapeutic effect while minimising disease activity and adverse effects.

The European League Against Rheumatism (EULAR) recommendations for the management of SLE support using antimalarials with or without glucocorticoids in the treatment of all patients with SLE, even without major organ involvement.⁶⁶ Although the use of corticosteroids remains the first line treatment, it is essential that every effort be made to minimise their dosage because of the extensive adverse effect profile. The early use of chemotherapeutic/cytotoxic agents and the development of newer, more

selective medications is aiming to improve control of the disease process while limiting adverse effects caused by the medication.

Corticosteroid therapy was used universally in our patients with childhood-onset SLE. This was supported by anti-malarials and further immunosuppressive therapy in the majority of patients. Historically not all patients were started on Chloroquine but in recent years this has been prescribed to all patients in line with international evidence based guidelines.

As most of our patients presented with major organ involvement, the use of further immunosuppressive agents in these patients is warranted, in particular in patients with lupus nephritis, where they have been shown to be effective against the progression to ESRD.⁶⁶⁻⁷¹ Long-term efficacy has been demonstrated for cyclophosphamide based regimens, but this has been associated with considerable adverse effects.^{72,73} Mycophenolate Mofetil (MMF) is an alternative treatment that was used in almost a third of this cohort. In recent trials, MMF has demonstrated similar efficacy, especially in patients with moderate to severe forms of lupus nephritis, with a more favourable toxicity profile.⁷⁴⁻⁷⁹

Only a few patients were treated with intravenous immunoglobulin therapy. Rituximab was used for one patient with Thrombotic Thrombocytopenic Purpura and severe renal disease.

Outcome

Outcome was assessed using three parameters: the SLICC/ACR DI, progression to ESRD and survival.

SLICC/ACR DI Scores. Reporting methods in many studies using the SLICC/ACR DI scores varied making it difficult to do any direct comparisons with our studies. However, it can be seen that other studies reported significant morbidity due to the therapy for the disease, as well as the disease process itself. This can be seen with cataracts, avascular necrosis (AVN) and muscular atrophy, mainly as side effects to prolonged corticosteroid use, being common indices scored.^{7,37,54,55} In our patients we

saw limited scores for the complications related to therapy, and most of our patients had scores related to the disease process, with renal disease being a prevalent factor in the SLICC/ACR DI scores. This could be related to short follow up time, the relatively young age of patients, as well as a therapeutic approach aimed at reducing corticosteroid exposure.

Despite many of our patients presenting with major organ involvement results of the SLICC/ACR DI were similar to other worldwide studies. With 58% of our patients having a SLICC/ACR DI score of one or more, indicating some degree of damage, this is comparable to other larger studies.^{7,37,54,80,81} However a large, multicentre world-wide study had only 50.5% having some degree of damage.³⁸ Some of these studies have reported higher median SLICC/ACR DI scores of 2 compared with our median score of 1.^{37,55,80} These studies have involved larger cohorts of patients, but with similar follow-up times. A larger study in Israel, where there is also a mixed ethnic population, showed better results, with 69% of their patients having no damage, with a mean SLICC/ACR DI score of 0.7 and a median score of 0.⁴¹ Better comparisons could be made if more patients were recruited in to our study. However, all of our patients were deemed unwell enough to be referred to our tertiary unit, maybe indicating that they are at the more extreme end of the disease spectrum, which can be supported by the high amount of major organ involvement at presentation.

It must also be remembered that although the SLICC/ACR DI has been validated for use in childhood-onset SLE, it does not cover all forms of damage that children or adolescents with SLE may develop over time, particularly effects on growth and development. It has been suggested that growth retardation and pubertal delay should be included in a paediatric version of the SLICC/ACR DI.³⁷

Dialysis and Transplant. The Red Cross War Memorial Children's Hospital is a referral unit for a large area of Southern Africa and we offer dialysis and transplant services. Although SLE was once regarded as a contraindication to transplantation, dialysis and renal transplantation are currently regarded as the treatment of choice for ESRD in childhood-onset SLE patients.^{66,67} Long-term patient and graft survival has been good in patients with SLE, and transplantation is the method of choice.⁸²⁻⁸⁴ A third of patients with renal involvement received dialysis for their kidney failure and

most of these patients (71%) received renal transplantation during the course of the illness. One of the patients who received dialysis died due to ESRD. All of the patients who received a kidney transplant are still alive, with all bar one of the patients having no further sequelae of the disease or the treatment of the disease according to the SLICC/ACR DI.

In Egypt, 5.3% of patients received renal dialysis, 5% of those from Israel and 2% of those from Canada.^{40,41,54} These numbers were all much lower than our 21.9% of patients, again indicating that our patients had more severe disease, especially in renal involvement.

In Egypt, it has been reported that 1.4% of their patients with renal disease received a renal transplantation.⁴⁰ This is much lower than our 23.8% of renal patients who went on to receive a renal transplantation. The fact that we have access to transplantation could explain why there is a better outcome amongst our patients, with renal transplantation being shown to be successful in children with SLE.⁸²

Mortality. In the last thirty years the prognosis of SLE presenting in childhood has improved dramatically. There is a bimodal pattern of mortality, either from initial disease activity or from complications relating to either the disease itself or from therapies used in the treatment of the disease.⁸⁵ In the early 1980's, survival at 5 years from onset in childhood-onset SLE was reported to be between 89-92% in Western countries.⁸⁶⁻⁸⁸ However, in developing nations, survival was much poorer, reported as low as 68% and 55.7% in Chile and Japan.^{89,90} This has improved to 95% and 95.9% in these nations respectively.

With the majority of our patients being followed up for more than 3 years (66%), our mortality rate in this small study of only 6.3% is comparable to studies from other developing nations, for example between 5% and 6% in Egypt, India and Chile.^{40,90,91} This is despite a large proportion of patients presenting with major organ involvement and a relatively high proportion of patients presenting with renal involvement, two factors that have been associated with poorer outcome.^{15-17,48,90}

Limitations

This study was limited in its analysis by the low patient numbers and the fact that it was a retrospective study. Larger patient numbers looked at in a prospective fashion are needed for more complete analysis of clinical manifestations and laboratory results. This would also allow trends and comparisons to be made with more confidence as well as looking in more depth at prognostic factors and outcomes.

Conclusion

This is a unique population group never before studied. Although the presenting features of childhood-onset SLE in our diverse population group were similar to other countries throughout the world, some key differences can be seen and no common thread can be clearly identified. Differences in the clinical expression of SLE in different populations may be explained by the presence of genetic, socioeconomic and environmental factors.

The age at onset, clinical manifestations and laboratory result at presentation of childhood-onset SLE in Cape Town were comparable to other reports from around the world, although each group of patients seems have subtle differences from the rest. SLE is a diverse disease, affecting many different organs of the body and it looks like no two groups of patients are identical in disease profile.

A large proportion of our patients presented with major organ involvement, agreeing with another South African study that our patients are most likely presenting later in the disease process. Renal disease was more likely in our younger patients and urinalysis of patient with suspected SLE is vital. Patients with positive anticardiolipin antibodies must also be closely screened for renal involvement.

Despite a lower age of onset and a high proportion of patients with major organ involvement at presentation the outcome and mortality in these patients was generally good. Earlier diagnosis, better treatment protocols and aggressive management of both lupus nephritis and infections have all contributed to the improved outcome in this severe disease.

More studies looking at childhood-onset SLE in Southern Africa should lead to a greater awareness of this complex disease and its severe initial manifestations.

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Part D – Appendices

1. Data collections sheet.
2. American College of Rheumatology diagnostic criteria.
3. Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index score.
4. Ethics approval and annual progress report renewal.
5. SAGE manuscript submission guidelines for Lupus journal.

Appendix 1. Data collection sheet.

Study number		Race Gender	m / f
DOB	/ /	Date First Presentation: Date Diagnosis SLE: Date Last Seen:	Duration Follow up
Clinical Data			
Height (centile): 1st	last:	Weight: 1st	last:
Features at presentation	Malar Rash Discoid Rash Photosensitivity Oral Ulcers Arthritis (2 or more joints) Serositis : Pleuritis pericarditis Renal Disorder: Persistent Proteinuria (3+or >0.5g/day) Cellular Casts Neurologic Disorder: Seizures (absence of other cause) Psychosis (absence of other cause) Hematologic Disorder: Hemolytic Anemia with reticulocytosis Leukopenia (<4000/mm ³) X2 occasions Lymphopenia (<15000/ mm ³) X2 occassions Immunologic Disorder: Positive Anti ds-DNA Positive anti SM nuclear antigen False Positive for syphillis Antinuclear Antibody: Hep2 Elisa Other manifestations not included above: CNS M/S CVS Skin Resp Eyes GIT Haem Renal Fever Reynauds Lymphadenopathy Weight loss		
Affected Systems throughout course (also state final outcome per system)	CNS M/S CVS Skin Resp Eyes GIT Haem Renal (see detailed box below)		

Serious Infections (requiring IV antibiotics or admission or prolonged treatment(>1week))	No of Infections during course of follow up: Positive Cultures Organisms:									
Renal Disease	Blood: Prot: Prot/Creat: 24hr protein Ceatinine/GFR:				1 st	1yr	5yr	Last		
	Biopsy: Grade Dialysis/transplant: Date:									
C3/C4	1 st	1yr	5yr	Last	ESR	1 st	1yr	5yr	Last	
ANA: Method:	1 st	1yr	5yr	Last	Anti ds DNA	1 st	1yr	5yr	last	
AntiCardiolipin LAC	1 st	Last:	Hb: WCC Plt	1 st	1yr	5yr	last			
SLEDAI	1st	1yr	5yr	last	SLICC	1st	1 yr	5yr	Last	
Treatment										
Steroids										
Azathioprine										
MMF										
Chloroquine										
Methotrexate										
Cyclophosphamide (Cumulative Dose)										
Polygam (Cumulative Doses)										
Rituximab (Cumulative Dose)										
Other										

Total Time on Therapy(days)

Steroids

AZA

MMF

Chloroquine

MTX

Comments and Outcome

Sustained remission:

Ongoing periods of active disease:

Deceased:

Cause of death:

Additional Comments

Appendix 2. 1997 Update of the 1982 American College of Rheumatology revised criteria for classification of systemic lupus erythematosus.


1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or pericarditis	<ol style="list-style-type: none"> 1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR 2. Pericarditis--documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	<ol style="list-style-type: none"> 1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed OR 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	<ol style="list-style-type: none"> 1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	<ol style="list-style-type: none"> 1. Hemolytic anemia--with reticulocytosis OR 2. Leukopenia--< 4,000/mm³ on ≥ 2 occasions OR 3. Lymphopenia--< 1,500/mm³ on ≥ 2 occasions OR 4. Thrombocytopenia--<100,000/mm³ in the absence of offending drugs
10. Immunologic disorder	<ol style="list-style-type: none"> 1. Anti-DNA: antibody to native DNA in abnormal titer OR 2. Anti-Sm: presence of antibody to Sm nuclear antigen OR 3. Positive finding of antiphospholipid antibodies on: <ol style="list-style-type: none"> 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. a positive test result for lupus anticoagulant using a standard method, or 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Appendix 3. Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus.*

Item		Score
Ocular (either eye)	Any cataract ever	1
	Retinal change or optic atrophy	1
Neuropsychiatric	Cognitive impairment or major psychosis	1
	Seizures requiring therapy for 6 months	1
	Cerebrovascular accident ever (score 2 if >1)	1 (2)
	Cranial or peripheral neuropathy (excluding optic)	1
	Transverse myelitis	1
Renal	Estimated or measured glomerular filtration rate <50%	1
	Proteinuria ≥ 3.5 gm/24hours OR	1
	End-stage renal disease (regardless of dialysis or transplant)	3
Pulmonary	Pulmonary hypertension (right ventricular prominence, or loud P2)	1
	Pulmonary fibrosis (physical and radiograph)	1
	Shrinking lung (radiograph)	1
	Pleural fibrosis (radiograph)	1
	Pulmonary infarction (radiograph)	1
Cardiovascular	Angina or coronary artery bypass	1
	Myocardial infarction ever (score 2 if >1)	1 (2)
	Cardiomyopathy (ventricular dysfunction)	1
	Valvular disease (diastolic murmur, or systolic murmur >3/6)	1
	Pericarditis for 6 months, or pericardiectomy	1
Peripheral Vascular	Claudication for 6 months	1
	Minor tissue loss (pulp space)	1
	Significant tissue loss ever (e.g. loss of digit or limb) (score 2 if >1)	1 (2)
	Venous thrombosis with swelling, ulceration or venous stasis	1
Gastrointestinal	Infarction or resection of bowel below duodenum, spleen, liver or gallbladder ever, for any cause (score 2 if >1 site)	1 (2)
	Mesenteric insufficiency	1
	Chronic peritonitis	1
	Stricture or upper gastrointestinal surgery ever	1
Musculoskeletal	Muscle atrophy or weakness	1
	Avascular necrosis (AVN) (score 2 if >1)	1 (2)
	Osteoporosis with fracture or vertebral collapse (excl AVN)	1
	Deforming or erosive arthritis (incl reducible deformities, excl AVN)	1
	Osteomyelitis	1
Skin	Scarring chronic alopecia	1
	Extensive scarring or panniculum other than scalp and pulp space	1
	Skin ulceration (excluding thrombosis) for >6 months	1
Other	Premature gonadal failure	1
	Diabetes (regardless of treatment)	1
	Malignancy (excluding dysplasia) (score 2 if >1 site)	1 (2)

* Damage (non reversible change, not related to active inflammation) occurring since the onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur 6 months apart to have score 2. The same lesion cannot be scored twice.

Appendix 4. Ethics approval and annual progress report/renewal.

 UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

12 February 2010

REC REF: 073/2010

Dr C Scott
Paediatrics

Dear Dr Scott

**PROJECT TITLE: CHARACTERISTICS OF CHILDHOOD SYSTEMIC LUPUS
ERYTHEMATOSUS IN CAPE TOWN, SOUTH AFRICA.**

Thank you for submitting your study to the Research Ethics Committee.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study including the following documentation.

Approval is granted for one year till the 10th December 2010.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that a form to undertake research at Red Cross Children's Hospital is available on the HREC's website.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.

S Thomas

UNIVERSITY OF CAPE TOWN
UNIVERSITEIT VAN KAPSTADFACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)

This serves as notification of annual approval, including any documentation described below.

<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	30/12/2013
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	29/11/2012

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	Original 12/10/10.		
HREC REF Number	073/2010	Current Ethics Approval was granted until	10/12/2010
Protocol title	Characteristics of Childhood Systemic Lupus Erythematosus in Cape Town, South Africa.		
Principal Investigator	Graeme Spittal		
Department / Office Internal Mail Address	PEDIATRIC DEPARTMENT, RED CROSS CHILDREN'S HOSPITAL		
1.1 Does this protocol receive US Federal funding?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

2. Protocol status (tick ✓)

<input type="checkbox"/>	Research-related activities are ongoing
<input checked="" type="checkbox"/>	Data collection is complete, data analysis only

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval	32
Total number of records or specimens collected, reviewed or stored since last progress report	32.
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

4. Signature

Signature of PI	Date	28/11/12
Signature of Supervisor (if PI is a student)	Date	28/11/12

26 July 2012

Page 1 of 1
(Note: Please complete the Closure form (FHS019) if the study is completed within the approval period)

FHS017

Appendix 5. SAGE manuscript submission guidelines for Lupus journal.

The only fully peer reviewed international journal devoted exclusively to lupus (and related disease) research. *Lupus* includes the most promising new clinical and laboratory-based studies from leading specialists in all lupus-related disciplines.

1. Peer review policy

The journal's policy is to obtain at least two independent reviews of each article. Lupus operates a conventional single-blind reviewing policy in which the reviewer's name is always concealed from the submitting author.

Referees will be encouraged to provide substantive, constructive reviews that provide suggestions for improving the work and distinguish between mandatory and non-mandatory recommendations.

All manuscripts accepted for publication are subject to editing for presentation, style and grammar. Any major redrafting is agreed with the author but the Editor's decision on the text is final.

2. Article types

Lupus is published fourteen times a year. The Editor will consider for publication all suitable papers dealing directly or indirectly with lupus or related diseases. The journal includes both clinical and non-clinical research papers. In addition to peer-reviewed (two referees) original papers, the journal also publishes editorials, reports, and letters.

EDITORIALS

Editorials are solicited by the Editor but suggestions for such material will be very welcome.

GRAND ROUNDS CASES

The purpose of a grand rounds submission is to educate the reader about one or more facets related to the disease lupus or of an autoimmune disease which is related to lupus. A clinicopathological conference can be submitted but this must have postmortem data and is usually a death conference or mortality conference.

Avoid extraneous material which has little bearing on the case at hand. The readers wish to learn about every facet of the case presented and not about other unrelated material.

The submitted case should contain:

Introduction - This should be no more than one or two short paragraphs and summarise what is about to be presented and the reasons why the case was chosen.

Case Presentation - This part contains a succinct narrative of the case itself. Figures, photographs and tables with data are welcome. Also encouraged are data on biopsies with illustrative materials if possible.

Discussion - The discussion should be a focused presentation of theory and/or pathogenetic data regarding the case.

Final Diagnosis - This should be only one sentence which gives the final diagnosis.

CONCISE REPORTS

These should be short investigative papers and reports organised in the same way as full-length manuscripts but which contain 2000 words or less, with no more than 3 figures or tables and up to 15 references.

CASE REPORTS

The Editor will consider for publication case reports that illustrate points not previously reported in the literature. They should not exceed two printed pages in length. The number of references should not exceed ten.

The number of case reports published will be strictly limited.

LETTERS TO THE EDITOR

Letters to the Editor are encouraged. They may deal with material in published papers or they may raise new issues. Short clinical or laboratory observations may also be presented as Letters.

Letters must contain no more than 500 words, 10 references, 1 table and/or 1 illustration. An abstract is not required and letters should not be divided into sections. Instructions for references, tables and figures are the same as for full length articles.

SUPPLEMENTS

The journal welcomes the opportunity of publishing supplements to regular issues of significant symposia providing the material represents original work not previously published.

Sponsored symposia should be fully discussed with the Editor prior to agreement to publish.

Faculty, subject matter and editorial content are all subject to the approval of the editorial office and the journal's integrity and reputation should in no way be compromised.

3. How to submit your manuscript

Before submitting your manuscript, please ensure you carefully read and adhere to all the guidelines and instructions to authors provided below. Manuscripts not conforming to these guidelines may be returned.

4. Journal contributor's publishing agreement

Before publication SAGE requires the author as the rights holder to sign a Journal Contributor's Publishing Agreement.

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reviewing procedure is unchanged. On acceptance of your article, you will be asked to let SAGE know directly if you are choosing SAGE Choice.

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Within your Journal Contributors Publishing Agreement you will be required to make a certification with respect to a declaration of conflicting interests. It is the policy of *Lupus* to require a declaration of conflicting interests from all authors enabling a statement to be carried within the paginated pages of all published articles.

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Any commercial or financial involvements that might represent an appearance of a conflict of interest need to be additionally disclosed in the covering letter accompanying your article to assist the Editor in evaluating whether sufficient disclosure has been made within the Conflict of Interest statement provided in the article.

6. Other conventions

6.1 Informed consent

Authors are required to ensure that the following guidelines are followed, as recommended by the International Committee of Medical Journal Editors.

Patients have a right to privacy that should not be infringed without informed consent. Identifying information, including patients' names, initials, or hospital numbers, should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that a patient who is identifiable be shown the manuscript to be published. Complete anonymity is difficult to achieve, however, and informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic pedigrees, authors should provide assurance that alterations do not distort scientific meaning and editors should so note.

When informed consent has been obtained it should be indicated in the submitted article.

Authors should identify individuals who provide writing/administrative assistance, indicate the extent of assistance and disclose the funding source for this assistance. Identifying details should be omitted if they are not essential.

6.2 Ethics

When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the Declaration of

Helsinki 1975, revised Hong Kong 1989. Do not use patients' names, initials or hospital numbers, especially in illustrative material. When reporting experiments on animals, indicate which guideline/law on the care and use of laboratory animals was followed.

7. Acknowledgements

Any acknowledgements should appear first at the end of your article prior to your Declaration of Conflicting Interests (if applicable), any notes and your References. All contributors who do not meet the criteria for authorship should be listed in an 'Acknowledgements' section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Authors should disclose whether they had any writing assistance and identify the entity that paid for this assistance.

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To comply with the guidance for Research Funders, Authors and Publishers issued by the Research Information Network (RIN), *Lupus* additionally requires all Authors to acknowledge their funding in a consistent fashion under a separate heading.

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Authors are asked to write their manuscripts in English. Spelling and phraseology should conform either to standard UK English or to standard American English and should be consistent throughout the paper.

The Summary should not exceed 200 words. It should be written in a style that conveys the essential message of the paper in abbreviated form.

The Introduction should assume that the reader is knowledgeable in the field and should therefore be as brief as possible.

In the Materials and methods section, methods that have been published in detail elsewhere should not be described in detail. SI units should be used throughout the text.

9.1 File types

Only electronic files conforming to the journal's guidelines will be accepted. Preferred formats for the text and tables of your manuscript are Word DOC, and tiff or jpeg for figures (ideally figures will use journal colours).

9.2 Journal Style

Lupus conforms to the SAGE house style.

9.3 Reference Style

Lupus adheres to the SAGE Vancouver reference style.

It is important that references comply with the style of the journal. Exhaustive lists should be avoided. References should follow the Vancouver format, listed (double-spaced) in numerical order corresponding to the order of citation in the text.

All authors should be quoted for papers with up to six authors; for papers with more than six authors, the first three only should be quoted followed by et al.

No issue numbers should be quoted.

Abbreviations for titles of medical periodicals should conform to those used in the latest editions of Index Medicus and Current Contents. The first and last page numbers for each reference should be provided. Abstracts and letters must be identified as such. Papers in press and papers already submitted for publication may be included in the list of references. No citation is required for work that is not yet submitted for publication. Personal communications may be allocated a number and included in the list of references in the usual way or simply referred to in the text. Authors must obtain permission from the individual concerned to quote his or her unpublished work.

Examples of References:

Journal article:

1 Derksen RHW, Bouma BN, Kater L. The association between the lupus anticoagulant and cerebral infarction in systemic lupus erythematosus. *Scand J Rheumatol* 1986; 15: 179-184.

Journal article, in press:

2 Mendonca LLF, Khamashta MA, Nelson-Piercy A, Hunt BJ, Hughes GRV. Nonsteroidal anti-inflammatory drugs as a possible cause for reversible infertility. *Rheumatology* (in press).

Journal article submitted for publication:

3 Khamashta MA, Cervera R, Asherson RA. Association of antibodies against phospholipids with heart valve disease in systemic lupus erythematosus (submitted for publication).

Complete book:

4 Wallace DJ, Dubois EL. *Dubois' Lupus Erythematosus*. Lea & Febiger, 1987, p 51.

Chapter in book:

5 Christian CL. Etiologic hypotheses for systemic lupus erythematosus. In: Lahita RG (ed) *Systemic Lupus Erythematosus*. Wiley, 1987, 65-79.

Abstract:

6 Valesini G, Luan FL, Falco M. Clonal analysis of affinity purified anticardiolipin antibodies. *Clin Exp Rheumatol* 1988; 6: 214 (abstract 102).

Letter to the Editor:

7 Sills EM. Systemic lupus erythematosus in a patient diagnosed as having Shulman disease. *Arthritis Rheum* 1988; 31: 694 (letter).

9.4. Manuscript Preparation

The text should be double-spaced throughout and with a minimum of 3cm for left and right hand margins and 5cm at head and foot. Text should be standard 10 or 12 point. SI units should be used throughout the text.

9.4.1 Keywords and Abstracts

The title, keywords and abstract are key to ensuring that readers find your article online through online search engines such as Google.

9.4.2 Corresponding Author Contact details

Provide full contact details for the corresponding author including email, mailing address and telephone numbers. Academic affiliations are required for all co-authors.

9.4.3 Guidelines for submitting artwork, figures and other graphics

TABLES

Each table should be numbered consecutively with an Arabic numeral. Each should have a separate caption or title. Methods not described in the text and abbreviations should be explained at the foot of the table. Footnotes should be designated by superior lower case letters (a, b, c etc). Vertical lines should not be inserted in the table. Tables must be referred to specifically in the text of the paper.

FIGURES

Lettering should be planned for 50% reduction; text should be readable after reduction. Figures should be referred to as Figure 1, Figure 2 etc. Figures must be referred to specifically in the text of the paper.

Images should be supplied as bitmap based files (i.e. with .tiff or .jpeg extension) with a resolution of at least **300 dpi** (dots per inch). Line art should be supplied as vector-based, separate .eps files (not as .tiff files, and not only inserted in the Word or pdf file), with a resolution of **600 dpi**. Images should be clear, in focus, free of pixilation and not too light or dark.

Colour photographs and Figures - Important information:

Colour photographs and Figures, when accepted, will be published online. In the printed version, they will be in black and white (unless colour prints are paid for). Authors who submit in colour must ensure that their figures are of the highest definition for the black and white version otherwise these may not be accepted. In particular immuno-fluorescent and histological figures, as well as skin rashes, must be paid for in colour or omitted from the manuscript and replaced in a descriptive format. If, together with your accepted article, you submit usable colour figures, these figures will appear in colour online regardless of whether or not these illustrations are reproduced in colour in the printed version. For specifically requested colour reproduction in print, you will receive information regarding the possible costs from SAGE after receipt of your accepted article.

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The journal may be able to host approved supplemental materials online, alongside the full-text of articles. Supplemental files will be subjected to peer-review alongside the article.

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